

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208447Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZEJULA safely and effectively. See full prescribing information for ZEJULA.

ZEJULA™ (niraparib) capsules, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ZEJULA is a poly(ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of 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)

DOSAGE AND ADMINISTRATION

- Recommended dose is 300 mg taken once daily with or without food. (2.1)
- Continue treatment until disease progression or unacceptable adverse reaction. (2.1, 2.2)
- For adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): MDS/AML occurred in patients exposed to ZEJULA, and some cases were fatal. Monitor patients for hematological toxicity and discontinue if MDS/AML is confirmed (5.1)

- Bone Marrow Suppression: Test complete blood counts weekly for the first month, monthly for the next 11 months and periodically thereafter for clinically significant changes. (5.2)
- Cardiovascular Effects: Monitor blood pressure and heart rate monthly for the first year and periodically thereafter during treatment with ZEJULA. Manage with antihypertensive medications as well as adjustment of the ZEJULA dose, if necessary. (5.3)
- Embryo-Fetal Toxicity: ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 10\%$) are thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue/asthenia, decreased appetite, urinary tract infection, AST/ALT elevation, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, nasopharyngitis, dyspnea, cough, rash, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TESARO at 1-844-4-TESARO or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed during treatment and for 1 month after receiving the final dose. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZEJULA™ is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

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.

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.

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.

2.2 Dose Adjustments for Adverse Reactions

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

Dose level	Dose
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.

Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	<ul style="list-style-type: none"> 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.
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

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 (5.1)].	
Platelet count <100,000/μL	<p>First occurrence:</p> <ul style="list-style-type: none"> 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.
	<p>Second occurrence:</p> <ul style="list-style-type: none"> 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 Hemoglobin <8 g/dL	<ul style="list-style-type: none"> Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/μL or hemoglobin returns to ≥9 g/dL. Resume ZEJULA at a reduced dose per Table 1. Discontinue ZEJULA if neutrophils and/or hemoglobin 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.*
Hematologic adverse reaction requiring transfusion	<ul style="list-style-type: none"> 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.

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue ZEJULA [see [Warnings and Precautions \(5.1, 5.2\)](#)].

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received ZEJULA. In Trial 1 (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.

5.2 Bone Marrow Suppression

Hematologic 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.

Do not start ZEJULA until patients have recovered from hematological toxicity caused by previous chemotherapy (\leq Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics [see [Dosage and Administration \(2.2\)](#)].

5.3 Cardiovascular Effects

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 Trial 1. Discontinuation due to hypertension occurred in <1% of patients.

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 \(2.2\)](#) and [Nonclinical Toxicology \(13.2\)](#)].

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to a pregnant woman [see [Clinical Pharmacology \(12.1\)](#)]. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see [Warnings and Precautions \(5.2\)](#) and [Nonclinical Toxicology \(13.1\)](#)]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib.

Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of ZEJULA [see [Use in Specific Populations \(8.1, 8.3\)](#)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia [see [Warnings and Precautions \(5.1\)](#)]
- Bone Marrow Suppression [see [Warnings and Precautions \(5.2\)](#)]
- Cardiovascular Effects [see [Warnings and Precautions \(5.3\)](#)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ZEJULA monotherapy 300 mg once daily has been studied in 367 patients with platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer in Trial 1 (NOVA). Adverse reactions in Trial 1 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 Trial 1 was 15%. The median exposure to ZEJULA in these patients was 250 days.

Table 4 and [Table 5](#) summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with 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				

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 %
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
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

	Grades 1-4		Grades 3-4	
	ZEJULA N=367 (%)	Placebo N= 179 (%)	ZEJULA N= 367 (%)	Placebo N= 179 (%)
Decrease in hemoglobin	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

The following adverse reactions and laboratory abnormalities have been identified in \geq 1 to $<$ 10% of the 367 patients receiving ZEJULA in the NOVA trial and not included in the table: tachycardia, peripheral edema, hypokalemia, bronchitis, conjunctivitis, gamma-glutamyl transferase increased, blood creatinine increased, blood alkaline phosphatase increased, weight decreased, depression, epistaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZEJULA can cause fetal harm when administered to pregnant women [see [Clinical Pharmacology \(12.1\)](#)]. There are no data regarding the use of ZEJULA in pregnant women to inform the drug-associated risk. ZEJULA has the potential to cause teratogenicity and/or embryo-fetal death since niraparib is genotoxic and targets actively dividing cells in animals and patients (e.g., bone marrow) [see [Warnings and Precautions \(5.2\)](#) and [Nonclinical Toxicology \(13.1\)](#)]. Due to the potential risk to a fetus based on its mechanism of action, animal developmental and reproductive toxicology studies were not conducted with niraparib. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. 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.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

ZEJULA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

A pregnancy test is recommended for females of reproductive potential prior to initiating ZEJULA treatment.

Contraception

Females

ZEJULA can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception treatment with ZEJULA and for at least for 6 months following the last dose.

Infertility

Males

Based on animal studies, ZEJULA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of ZEJULA have not been established in pediatric patients.

8.5 Geriatric Use

In Trial 1 (NOVA), 35% of patients were aged ≥ 65 years and 8% were aged ≥ 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.

8.6 Renal Impairment

No dose adjustment is necessary for patients with mild (CLcr:60 to 89 mL/min) to moderate (CLcr:30 to 59 mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of ZEJULA in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

8.7 Hepatic Impairment

No dose adjustment is needed in patients with mild hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria. The safety of ZEJULA in patients with moderate to severe hepatic impairment is unknown.

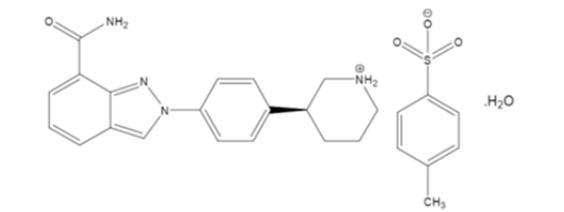
10 OVERDOSAGE

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.

11 DESCRIPTION

Niraparib is an orally available poly(ADP-ribose) polymerase (PARP) inhibitor.

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). The molecular formula is $C_{26}H_{30}N_4O_5S$ and it has a molecular weight of 510.61 amu. The molecular structure is shown below:



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. The inactive ingredients in the *capsule fill* are magnesium stearate and lactose monohydrate. The *capsule shell* consists of titanium dioxide, gelatin in the white capsule body; and FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 and gelatin in the purple capsule cap. The *black printing ink* consists of shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide. The *white printing ink* consists of shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, sodium hydroxide, povidone and titanium oxide.

12 CLINICAL PHARMACOLOGY

12.1 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 tumor cell lines with or without deficiencies in *BRCA1/2*. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA1/2* and in human patient-derived xenograft tumor models with homologous recombination deficiency that had either mutated or wild type *BRCA1/2*.

12.2 Pharmacodynamics

The pharmacodynamic response of niraparib has not been characterized.

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 *Nonclinical Toxicology (13.2)*].

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 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.

12.3 Pharmacokinetics

Following a single-dose administration of 300 mg niraparib, the mean (\pm SD) peak plasma concentration (C_{max}) was 804 (\pm 403) ng/mL. The systemic exposures (C_{max} and AUC) of niraparib increased in a dose proportional manner with daily doses ranging 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%. Following oral administration of niraparib, peak plasma concentration, C_{max} , is reached within 3 hours.

Concomitant administration 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 pharmacokinetics of niraparib.

Distribution

Niraparib is 83.0% bound to human plasma proteins. The average (\pm SD) apparent volume of distribution (V_d/F) was 1220 (\pm 1114) L. In a population pharmacokinetic analysis, the V_d/F of niraparib was 1074 L in cancer patients.

Elimination

Following multiple daily doses of 300 mg niraparib, the mean half-life ($t_{1/2}$) is 36 hours. In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.

Metabolism

Niraparib is metabolized primarily by carboxylesterases (CEs) to form a major inactive metabolite, which subsequently undergoes glucuronidation.

Excretion

Following administration of a single oral 300 mg dose of radio-labeled niraparib, the average percent recovery of the administered dose over 21 days was 47.5% (range 33.4% to 60.2%) in urine, and 38.8% (range 28.3% to 47.0%) in feces. In pooled samples collected over 6 days, unchanged niraparib accounted for 11% and 19% of the administered dose recovered in urine and feces, respectively.

Specific Populations

Age (18 to 65 years old), race/ethnicity, and 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.

The effect of moderate or severe hepatic impairment on the pharmacokinetics of niraparib is unknown.

Drug Interaction Studies

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 CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Induction of CYPs: Neither niraparib nor M1 is a CYP3A4 inducer. Niraparib weakly induces CYP1A2 in vitro.

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 BCRP, but does not inhibit P-gp or 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 cation transporter 1 (OCT1), organic anion transporter 1 (OAT1), 3 (OAT3), or organic cation transporter 2 (OCT2).

Substrate of transporter systems: Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Niraparib is not a substrate of bile salt export pump (BSEP). The M1 metabolite is not a substrate of P-gp, BCRP, or BSEP. 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).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with niraparib.

Niraparib 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. Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test.

Fertility studies in animals have not been conducted with niraparib. In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months duration in rats and dogs. Reduced sperm, spermatids and germ cells in epididymides and testes were observed at doses ≥ 10 mg/kg and ≥ 1.5 mg/kg in rats and dogs, respectively. These dose levels resulted in systemic exposures approximately 0.3 and 0.012 times, respectively, the human exposure (AUC_{0-24hr}) at the recommended dose of 300 mg daily. There was a trend toward reversibility of these findings 4 weeks after dosing was stopped.

13.2 Animal Toxicology and/or Pharmacology

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 IC_{50} values that were lower than the C_{min} at steady-state in patients receiving the recommended dose. Niraparib has the potential to cause effects in patients related to inhibition of these transporters (e.g., cardiovascular or CNS).

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.

In addition, niraparib crossed the blood-brain barrier in rats and monkeys following oral administration. The cerebrospinal fluid (CSF):plasma C_{max} ratios of niraparib administered at 10 mg/kg orally to two Rhesus monkeys were 0.10 and 0.52.

14 CLINICAL STUDIES

Trial 1 (NOVA) was a double-blind, placebo-controlled trial in which 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 BRCAAnalysis CDx. Patients with deleterious or suspected deleterious germline *BRCA*

mutations (gBRCAm) were assigned to the germline *BRCA* mutated (gBRCAmut) cohort (n=203), and those without germline *BRCA* mutations were assigned to the non-gBRCAmut cohort (n=350).

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.

The median age of patients ranged from 57-64 years among patients treated with ZEJULA and 58-67 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. Approximately 40% of patients had 3 or more lines of treatment.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to ZEJULA as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort (Table 6, and Figures 1 and 2).

Table 6: Efficacy Results - Study 1 (IRC Assessment^a, Intent-To-Treat Population)				
	gBRCAmut Cohort		non-gBRCAmut 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 gBRCAmut Cohort Based on IRC Assessment (ITT Population, N=203)

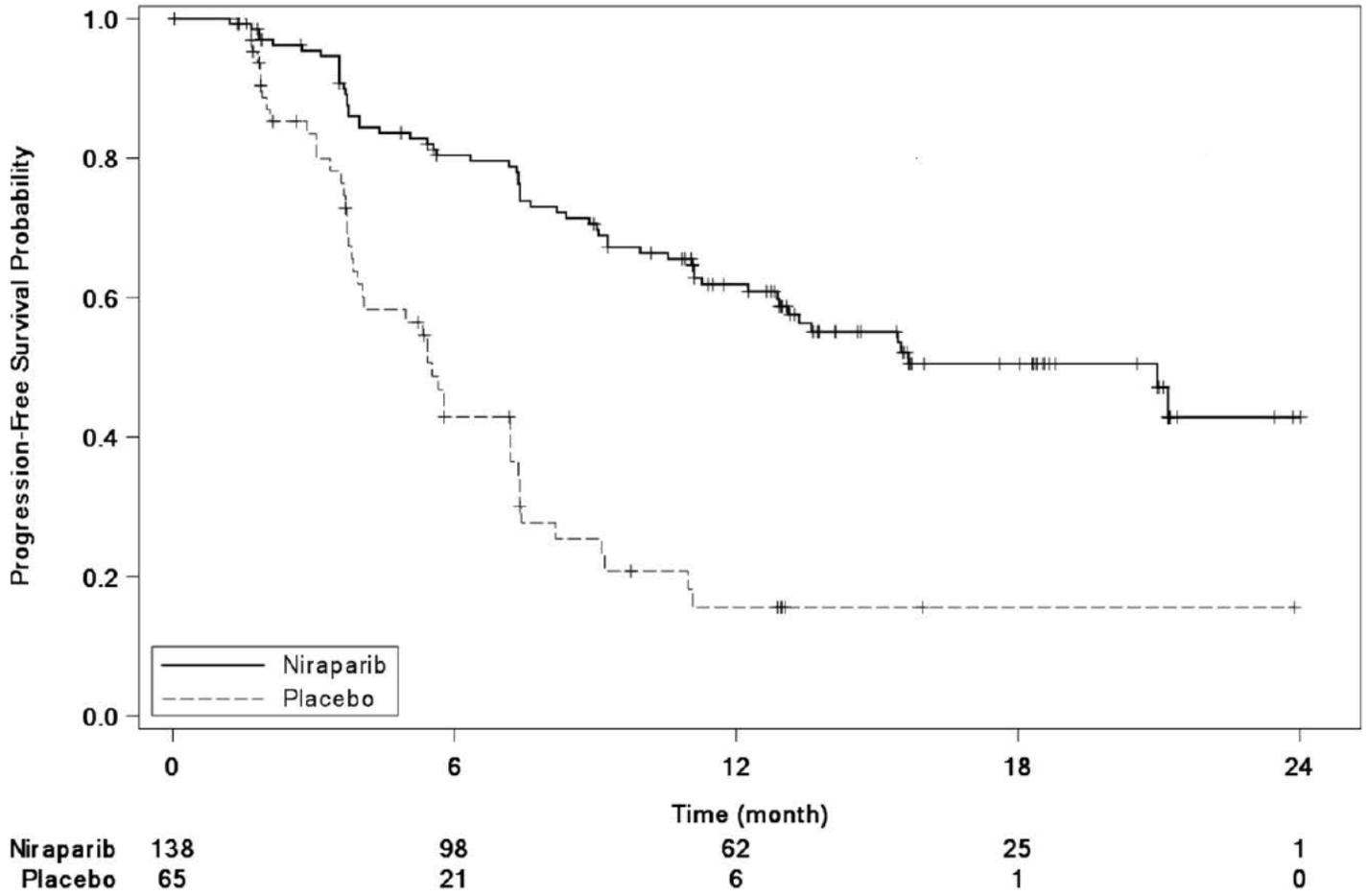
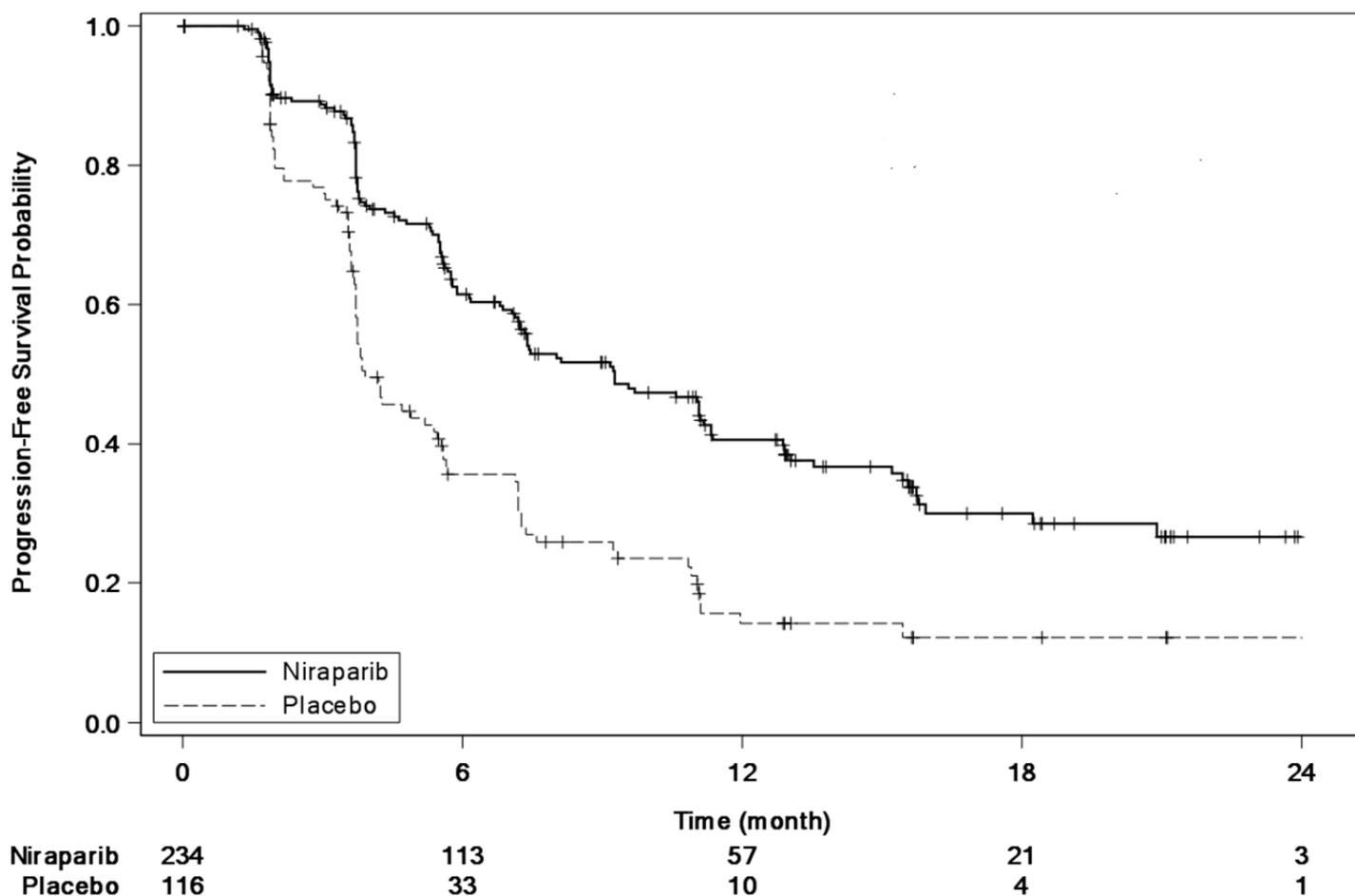


Figure 2: Kaplan-Meier Plot for Progression-Free Survival in the Non-gBRCAmut Cohort Overall Based on IRC Assessment (ITT Population, N=350)



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

16 HOW SUPPLIED/STORAGE AND HANDLING

ZEJULA is available as capsules having a white body printed with “100 mg” in black ink, and a purple cap printed with “Niraparib” in white ink.

Each capsule contains 100 mg of niraparib free base.

ZEJULA capsules are packaged as 90-count bottles

NDC 69656-103-90

Store at 20° to 25°C (68° to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling ([Patient Information](#)).

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) which has been reported in patients treated with ZEJULA [see [Warnings and Precautions \(5.1\)](#)].

Bone Marrow Suppression

Advise patients that periodic monitoring of their blood counts is required. Advise patients to contact their healthcare provider for new onset of bleeding, fever, or symptoms of infection [see [Warnings and Precautions \(5.2\)](#)].

Cardiovascular Effects

Advise patients to undergo monthly blood pressure and heart rate monitoring for the first year of treatment and then periodically thereafter and to contact their healthcare provider if blood pressure is elevated [see [Warnings and Precautions \(5.3\)](#)].

Dosing Instructions

Inform patients on how to take ZEJULA [see [Dosage and Administration \(2.1\)](#)]. ZEJULA should be taken once daily. Instruct patients that if they miss a dose of ZEJULA, not to take an extra dose to make up for the one that they missed. They should take their next dose at the regularly scheduled time. Each capsule should be swallowed whole. ZEJULA may be taken with or without food. Bedtime administration may be a potential method for managing nausea.

Embryo-Fetal Toxicity

Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [see [Warnings and Precautions \(5.4\)](#) and [Use in Specific Populations \(8.1\)](#)].

Contraception

Advise females of reproductive potential to use effective contraception during treatment with ZEJULA and for at least 6 months after receiving the last dose [see [Use in Specific Populations \(8.3\)](#)].

Lactation

Advise patients not to breastfeed while taking ZEJULA and for 1 month after the last dose [see [Use in Special Populations \(8.2\)](#)].

Manufactured for: TESARO, Inc. 1000 Winter St., #3300, Waltham, MA 02451

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PATIENT INFORMATION
ZEJULA™ (zuh-JOO-luh)
(niraparib)
capsules

What is the most important information I should know about ZEJULA?

ZEJULA may cause serious side effects including:

- **Bone marrow problems called Myelodysplastic Syndrome (MDS) or a type of cancer of the blood called Acute Myeloid Leukemia (AML).** Some people who have ovarian cancer and who have received previous treatment with chemotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with ZEJULA. MDS or AML may lead to death. If you develop MDS or AML, your healthcare provider will stop treatment with ZEJULA.

Symptoms of low blood cell counts (low red blood cells, low white blood cells, and low platelets) are common during treatment with ZEJULA, but can be a sign of serious bone marrow problems, including MDS or AML. Symptoms may include:

- weakness
- feeling tired
- weight loss
- frequent infections
- fever
- shortness of breath
- blood in urine or stool
- bruising or bleeding more easily

Your healthcare provider will do blood tests to check your blood cell counts:

- before treatment with ZEJULA
 - weekly for the first month of treatment with ZEJULA
 - every month for the next 11 months, then as needed during treatment with ZEJULA
- **High blood pressure.** High blood pressure is common during treatment with ZEJULA, and can become serious. Your healthcare provider will check your blood pressure and heart rate monthly for the first year and as needed thereafter during your treatment with ZEJULA.

See **“What are the possible side effects of ZEJULA?”** for more information about side effects.

What is ZEJULA?

ZEJULA is a prescription medicine used for the maintenance treatment of adults with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, when the cancer comes back. ZEJULA is used after the cancer has responded (complete or partial response) to treatment with platinum-based chemotherapy.

It is not known if ZEJULA is safe and effective in children.

Before taking ZEJULA, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- are pregnant or plan to become pregnant. ZEJULA can harm your unborn baby and may cause loss of pregnancy (miscarriage).
 - If you are able to become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with ZEJULA.
 - Females who are able to become pregnant should use effective birth control

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(niraparib)
capsules

(contraception) during treatment with ZEJULA and for 6 months after the last dose of ZEJULA. Talk to your healthcare provider about birth control methods that may be right for you.

- Tell your healthcare provider right away if you become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ZEJULA passes into your breast milk. Do not breastfeed during treatment with ZEJULA and for 2 weeks after the last dose of ZEJULA. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take ZEJULA?

- Take ZEJULA exactly as your healthcare provider tells you to.
- Take ZEJULA 1 time each day, at the same time each day.
- ZEJULA may be taken with or without food.
- ZEJULA capsules should be swallowed whole.
- Taking ZEJULA at bedtime may help relieve any nausea symptoms you may have.
- Do not stop taking ZEJULA without first talking with your healthcare provider.
- If you miss a dose of ZEJULA, take your next dose at your scheduled time. Do not take an extra dose to make up for a missed dose.
- If you vomit after taking a dose of ZEJULA, do not take an extra dose. Take your next dose at your scheduled time.
- If you take too much ZEJULA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ZEJULA?

ZEJULA can cause serious side effects, including:

- See **“What is the most important information I should know about ZEJULA?”**

The most common side effects of ZEJULA include:

- | | |
|-------------------------------|--|
| ● heart not beating regularly | ● changes in liver function blood tests |
| ● nausea | ● pain in your joints, muscles, and back |
| ● constipation | ● headache |
| ● vomiting | ● dizziness |
| ● pain in the stomach area | ● change in the way food tastes |
| ● mouth sores | ● trouble sleeping |
| ● diarrhea | ● anxiety |
| ● indigestion or heartburn | ● sore throat |
| ● dry mouth | ● shortness of breath |
| ● tiredness | ● cough |
| ● loss of appetite | ● rash |
| ● urinary tract infection | |

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with

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ZEJULA, if you have certain side effects.

These are not all the possible side effects of ZEJULA. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZEJULA?

Store ZEJULA at room temperature between 68° to 77°F (20° to 25°C).

Keep ZEJULA and all medicines out of the reach of children.

General information about the safe and effective use of ZEJULA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZEJULA for a condition for which it was not prescribed. Do not give ZEJULA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ZEJULA that is written for health professionals.

What are the ingredients in ZEJULA?

Active ingredient: niraparib

Inactive ingredients:

Capsule fill: magnesium stearate and lactose monohydrate

Capsule shell: titanium dioxide and gelatin in the white capsule body and FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 and gelatin in the purple capsule cap.

The black printing ink: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide.

The white printing ink: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, sodium hydroxide, povidone and titanium oxide.

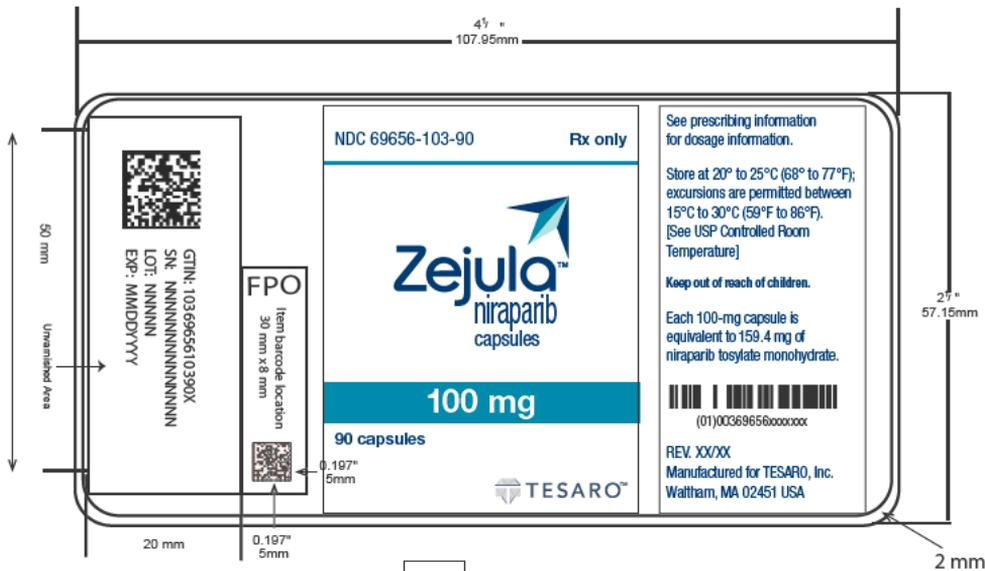
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For more information, call 1-844-483-7276 or go to www.tesarobio.com

This Patient Information has been approved by the U.S. Food and Drug Administration.

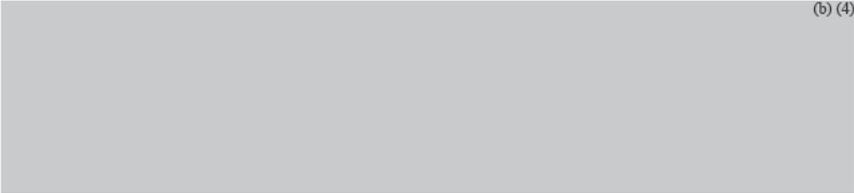
Issued: March 2017



 Copy limits

175cc Bottle Label - Size 4.25" x 2.25" (+/- 1/32")
 6 pt font
 10 mm x 10 mm 2D code

Colors



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/s/

RICHARD PAZDUR
03/27/2017