Drug Monograph

A - Drug Name

niraparib

COMMON TRADE NAME(S): Zejula

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B - Mechanism of Action and Pharmacokinetics

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, and acts to increase the formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased cytotoxicity was observed in tumor cell lines with or without deficiencies in BRCA1/2.

Absorption	Bioavailability	~73%
	Effects with food	Administration with a high-fat, high-calorie meal resulted in a 22% decrease in C_{max} compared to fasted conditions. However, food did not significantly affect the AUC.
	Peak plasma levels	C_{max} is reached in approximately 3 hours.
Distribution	Cross blood brain barrier?	Yes (in pre-clinical models)
	PPB	83%
Metabolism	Niraparib is metabolized by carboxylesterases.	
	Inactive metabolites	Yes

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	Active metabolites	No
Elimination	Half-life	48 to 51 hours (approximately 2 days)
	Feces	Average 38.8%; 18.7% unchanged drug from pooled samples collected over 6 days
	Urine	Average 47.5%; 11% unchanged drug from pooled samples collected over 6 days

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C - Indications and Status

- Epithelial ovarian cancer
- Fallopian tube cancer
- Primary peritoneal cancer

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following table lists adverse effects that occurred in ≥ 10% of patients in a phase III placebo-controlled study for the first-line maintenance treatment of advanced ovarian cancer where patients received an individualized starting dose of niraparib. It also includes severe, life-threatening and post-marketing adverse effects from other sources. Adverse effects marked with "^" were observed in maintenance treatment of recurrent ovarian cancer.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (17%) (9% severe)	E D L
	Palpitations (10%) ^	E
Dermatological	Photosensitivity (<10%)	E
Gastrointestinal	Abdominal pain (28%)	E
	Anorexia (19%)	E
	Constipation (33%)	E

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	Diarrhea (14%)	E
	Dyspepsia (18%) ^	E
	GI obstruction (3%) (severe)	E
	Mucositis (20%) ^	E
	Nausea, vomiting (53%) (generally mild)	I E
General	Fatigue (48%)	E
Hematological	Myelosuppression ± infection (54%) (including anemia) (21% severe)	E
Hepatobiliary	↑ LFTs (8%)	E
Hypersensitivity	Hypersensitivity (<10%) (including anaphylaxis)	I E
Musculoskeletal	Musculoskeletal pain (37%)	E
Neoplastic	Leukemia (secondary) (<1%)	E D L
Nervous System	Cognitive disturbance (<10%) (including hallucinations)	E
	Dizziness (11%)	E
	Dysgeusia (10%) ^	E
	Headache (22%)	E
	Insomnia (21%)	E
	Posterior reversible encephalopathy syndrome (PRES) (<1%)	E
Renal	Other - acute kidney injury (12%) (<1% severe, including increased creatinine/urea, renal failure)	E
Reproductive and breast disorders	Hot flashes (>10%)	E D
Respiratory	Cough, dyspnea (19%)	E
	Pneumonitis (<1%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for niraparib include myelosuppression ± infection, nausea/vomiting, fatigue, musculoskeletal pain, constipation, abdominal pain, headache, insomnia and mucositis.

Thrombocytopenia was commonly reported, with a median time of 22 days (ranging from 15 to 335 days) from the first niraparib dose to onset, and a median duration 6 days (ranging from 1 to 374 days).

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Hypertension and **hypertensive crisis** have been reported but rarely lead to treatment discontinuation. The median time from the first niraparib dose to onset of grade 3 or 4 hypertension was 43 days (ranging from 1 to 531 days), with a median duration 12 days (ranging from 1 to 61 days).

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) including fatal cases, have been rarely reported. The duration of niraparib treatment prior to the development of MDS/AML varied from <1 month to approximately 5 years. All patients had received prior chemotherapy with platinum-based regimens and/or other DNA-damaging agents, including radiotherapy.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients should have recovered from hematologic toxicities (≤ grade 1) from previous chemotherapy prior to initiating niraparib treatment.

Existing hypertension should be adequately controlled before initiating niraparib treatment.

Adults:

Epithelial ovarian, fallopian tube, or primary peritoneal cancer:

Patients <77 kg **or** with a platelet count <150 x 10^9/L:*

Oral: 200 mg Daily

Patients ≥77 kg **and** with a platelet count ≥150 x 10^9/L:*

Oral: 300 mg Daily

*based on pCODR, Berek et al.

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Dosage with Toxicity:

Dose Level	Niraparib Dose (mg/day)	
0	200	300
-1	100	200
-2	Discontinue	100
-3		Discontinue

Toxicity	Criteria	Action
Platelet count <100 x 10^9/L	First occurrence	Hold. Monitor blood counts weekly* Resume at same dose or at 1 dose level ↓. If platelet count was <75 x 10^9/L, resume at 1 dose level ↓.
	Second occurrence	Hold. Monitor blood counts weekly.* Resume at 1 dose level ↓.
Neutrophil <1 x 10^9/L		Hold. Monitor blood counts weekly.* Resume at 1 dose level ↓.
Hemoglobin <80 g/L		Hold. Monitor blood counts weekly.* Resume at 1 dose level ↓.
Hematologic adverse reaction requiring transfusion or hematopoietic growth factor support		Hold. Consider platelet transfusion for platelets ≤10 x 10^9/L. If other risk factors are present (e.g., coadministration of anticoagulation or antiplatelet drugs), consider interruption of concurrent therapy and/or transfuse at a higher platelet count. Resume at 1 dose level ↓.

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Signs and symptoms of myelodysplastic syndrome or acute myeloid leukemia (MDS/AML)	Any	If MDS/AML is confirmed, discontinue
Hypertension	Not adequately controlled with antihypertensive therapy Or Hypertensive crisis	Discontinue
Signs and symptoms of Posterior Reversible Encephalopathy Syndrome (PRES)	Any	Treat specific symptoms and discontinue
All other non-hematologic toxicities that persists despite treatment/prophylaxis	≥ Grade 3	Hold.* Resume at same dose or at 1 dose level ↓.

*Do not restart until platelets ≥100 x 10^9/L, ANC ≥1.5 x 10^9/L, Hb ≥90 g/L and other toxicities have resolved. Discontinue if toxicities have not recovered within 28 days of dose interruption. If blood parameters remain abnormal after 28 days, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Dosage with Hepatic Impairment:

Hepatic Impairment	**Bilirubin**		**AST**	**Niraparib Dose**
Mild	≤1.5xULN	and	any	No dose adjustment required
	≤ULN	and	>ULN	
Moderate	>1.5 to 3 xULN	and	any	↓ 1 dose level
Moderate or Severe	>3xULN	and	any	Has not been studied

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Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Niraparib Dose
≥ 30	No dose adjustment required
< 30 or ESRD	Has not been studied

Dosage in the elderly:

No dose adjustment required. No overall differences in safety and effectiveness of niraparib were observed between patients ≥ 65 years old and younger but greater sensitivity of some older patients cannot be ruled out.

Dosage based on ethnicity:

No dose adjustment required. Analyses suggested that race/ethnicity had no clinically significant effect on the pharmacokinetics of niraparib.

Children:

The safety and effectiveness of niraparib in pediatric patients have not been established.

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F - Administration Guidelines

- Niraparib should be taken with or without food at approximately the same time each day. (Bedtime administration may help manage nausea).
- The dose should be swallowed whole, not chewed, crushed, or split.
- If a dose of niraparib is missed, patients should take the next dose at the regularly scheduled time. Patients should not take an additional dose if vomiting or missed doses occur.
- Store at a temperature up to 25°C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to the drug or to any of its components or components of the container.

Other Warnings/Precautions:

- Niraparib has moderate influence on the ability to drive or use machines. Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery due to fatigue and dizziness.
- Patients should be counselled to avoid sun exposure when possible while on treatment.
- Niraparib capsules contain tartrazine (FD&C Yellow #5), which may cause allergic-type reactions.
- Niraparib capsules and tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Phototoxicity: Possible

Pregnancy and Lactation:

- Genotoxicity: Yes
- Clastogenicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Probable
- Pregnancy:
  Niraparib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for **6 months** after the last dose.
- Breastfeeding:
  Breastfeeding is **contraindicated** during treatment and for **1 month** after the last dose.
- Fertility effects: Probable
  Documented in animal studies with male animals

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H - Interactions

No formal drug interaction studies have been performed with niraparib.

In vitro, niraparib is a:

- weak inducer of CYP1A2
- weak inhibitor of BCRP, P-gp and OCT1
- inhibitor of MATE-1 and -2
- substrate of P-gp and BCRP

In vivo, niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs).

The potential of niraparib on intestinal CYP3A4 inhibition has not been established.

Caution is recommended when niraparib is combined with active substances with CYP3A4/1A2-dependent metabolism, that undergo uptake transport by OCT1 or with known inhibitors or inducers of carboxylesterases and conjugation (UGT) pathways.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and weekly for the first month of treatment then monthly for the next 11 months and as clinically indicated
Blood pressure and heart rate	Baseline and at minimum weekly for the first 2 months of treatment, then monthly for the first year and as clinically indicated (More frequent monitoring may be required in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension)
Clinical toxicity assessment for infection, hypersensitivity, fatigue, musculoskeletal pain, hot flashes, secondary malignancy, GI, cardiovascular, neurologic and respiratory effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- niraparib - For the maintenance treatment of newly diagnosed or recurrent high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, according to clinical criteria

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K - References

Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. Ann Oncol 2018 Aug 1;29(8):1784-92.

González-Martín A et al. PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402.

Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016 Dec 1;375(22):2154-64.

pCODR expert review committee: final recommendation. Niraparib (maintenance for first-line advanced ovarian cancer), April 2021.

pCODR expert review committee: final recommendation. Niraparib (maintenance for recurrent ovarian cancer), September 2020.

Prescribing Information: Zejula (niraparib). Tesaro Inc. August 2017.

Product Monograph: Zejula (niraparib). GlaxoSmithKline Inc. June 2, 2022.

March 2025 Updated Pregnancy/Lactation section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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