DRUG NAME: Niraparib

SYNONYM(S): MK-4827[1]

COMMON TRADE NAME(S): ZEJULA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Niraparib is a selective inhibitor of enzymes of the poly (ADP-ribose) polymerase family (e.g. PARP-1 and PARP-2) Binding to PARP inhibits single-stranded DNA base excision repair and creates PARP-DNA complexes that lead to double-stranded DNA breaks, ultimately causing cell death in tumours that cannot repair double-stranded breaks reliably. Niraparib-induced cytotoxicity has been observed in tumour cell lines with or without mutations in BRCA 1/2. Niraparib is an immunosuppressive agent.[2,3]

PHARMACOKINETICS:

Oral Absorption	absolute bioavailability = 73%; C_{max} = 3 hours food effect: high-fat, high-calorie food intake reduces C_{max} by 22%	
Distribution	highly bound to serum albumin	
	cross blood brain barrier?	yes
	volume of distribution	1074 L
	plasma protein binding	83%
Metabolism	metabolized by carboxylesterases	
	active metabolite(s)	no information found
	inactive metabolite(s)	M1 (major), M10
Excretion	multiple pathways including liver metabolism, hepatobiliary excretion, and renal elimination	
	urine	47.5%
	feces	38.8%
	terminal half life	36-51 h
	clearance	16.2 L/h

Adapted from standard reference[2,3] unless specified otherwise.

USES:

Primary uses:
*Ovarian cancer

Other uses:
Prostate cancer[3]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- ***hypertension and hypertensive crisis*** have been reported; preexisting hypertension should be well controlled prior to treatment[4]
- ***myelodysplastic syndrome/acute myeloid leukemia*** (MDS/AML) have been reported in patients who have received niraparib[5]

Special populations: Patients with ***low body weight*** may experience more grade 3 or 4 adverse drug reactions than patients with higher body weight; dose reduction may be required.[2,4]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Niraparib is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,3]

Fertility: In animal studies, reduced spermatogenesis, small testes, and germ cell depletion (in the testes and epididymides) were observed at lower exposures than those seen following human clinical exposure. There was a trend towards reversibility of these findings four weeks after the last dose.[2,3]

Pregnancy: Reproductive studies have not been conducted; however, based on its mechanism of action, niraparib may cause fetal harm if used during pregnancy. Niraparib is genotoxic and actively targets dividing cells, therefore, it has the potential to cause teratogenicity and embryo-fetal death. Women of childbearing potential should use contraception during treatment and for at least one month, and up to six months, following the last dose.[2,3,1]

Breastfeeding is not recommended due to potential secretion into breast milk. Women should wait at least one month following the last dose before breastfeeding.[2,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia (see paragraph following **Side Effects** table)	***anemia*** (50-64%, severe 23-31%)
	leukopenia (17-28%, severe 5%)
	neutropenia (20-42%, severe 13-21%)
	pancytopenia (<1%)
	thrombocytopenia (52-66%, severe 21-39%)
cardiac	***cardiac arrest*** (severe <2%); fatal events reported
	palpitations (10%)
	tachycardia (5-7%)
gastrointestinal	*emetogenic potential:* moderate[8]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (33-35%, severe 2-7%)
	constipation (31-40%, severe <5%)
	diarrhea (17-20%, severe <1%)
	dry mouth (10%, severe <1%)
	dyspepsia (18%)
	intestinal perforation (severe <1%); fatal events reported
	mucositis (20%, severe <1%)
	nausea (53-74%, severe 1-10%)
	small intestinal obstruction (severe 3-7%)
	vomiting (17-44%, severe <8%)
general disorders and administration site conditions	***fatigue*** (48-57%, severe 3-8%)
	peripheral edema (6%)
immune system	hypersensitivity, including anaphylaxis (<1%)
infections and infestations	conjunctivitis (1-2%)
	urinary tract infection (12-15%, severe <2%)
investigations	alkaline phosphatase increase (4-11%, severe <2%)
	ALT/AST increase (10-14%, severe 1-4%)
	creatinine increase (6%)
	gamma-glutamyl transferase increase (2-7%, severe <4%)
	weight decrease (3-4%)
metabolism and nutrition	appetite decrease (19-27%, severe <2%)
	hypokalemia (5-6%, severe 1%)
	hypomagnesemia (11%)
musculoskeletal and connective tissue	arthralgia (13%, severe <1%)
	back pain (18%, severe <1%)
	musculoskeletal pain (29-39%, severe 1-3%)
	myalgia (19%, severe <1%)
neoplasms	***myelodysplastic syndrome/acute myeloid leukemia*** (1%); see paragraph following **Side Effects** table
nervous system	dizziness (11-19%)
	dysgeusia (10%)
	headache (19-26%, severe <1%)
	posterior reversible encephalopathy syndrome (<1%); see paragraph following **Side Effects** table
psychiatric	anxiety (11%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	confusion/disorientation (<1%, severe <1%)
	cognitive impairment (<2%)
	depression (5-6%, severe <1%)
	hallucination (<1%, severe <1%)
	insomnia (21-27%, severe <1%)
renal and urinary	acute kidney injury (12-17%, severe <1%)
respiratory, thoracic and mediastinal	bronchitis (3-5%)
	cough (13-18%)
	dyspnea (18-22%, severe <3%)
	epistaxis (5%, severe <1%)
	nasopharyngitis (23%)
	non-infectious pneumonitis (<1%)
	pleural effusion (severe <1%); fatal events reported
skin and subcutaneous tissue	photosensitivity (6-9%, severe <1%)
	rash (21%, severe <1%)
vascular	hot flashes (>10%) [4]
	hypertension, hypertensive crisis (14-20%, severe 5-9%); see paragraph following **Side Effects** table

Adapted from standard reference[2-4,9] unless specified otherwise.

Hematologic toxicities (e.g., grade ≥3 thrombocytopenia, anemia, and neutropenia) have been reported; therefore, blood parameters should be monitored closely. In patients who have received prior myelosuppressive treatments, delay initiation of niraparib until blood counts have recovered. During treatment, monitor blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter as clinically indicated. Hold niraparib for hematologic toxicity and discontinue if hematologic toxicity does not resolve within four weeks of treatment interruption. Further investigations such as bone marrow analysis and blood cytogenic analysis are recommended if blood counts fail to recover.[2,3,10]

Hypertension *and* ***hypertensive crisis*** have been reported with niraparib and onset may be as early as one day after first dose. Monitor blood pressure and heart rate at least weekly for the first two months of treatment, then monthly for the first year, and periodically thereafter as clinically indicated. Patents with preexisting cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension should be monitored more closely. Clinically manage hypertension with antihypertensive medications and niraparib dose adjustment as needed.[2,3,1]

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) may occur and fatal cases have been reported. Time to onset has varied from two weeks to five years, and may occur after treatment discontinuation. Possible risk factors for MDS/AML include: previous platinum chemotherapy, and/or other DNA damaging agents and radiotherapy. Permanently discontinue niraparib if MDS/AML is confirmed.[2,3,10]

Posterior reversible encephalopathy syndrome (PRES) has been reported with symptoms including seizures, headache, altered mental status, visual disturbance, and/or cortical blindness. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. If PRES is confirmed, discontinue niraparib.[4]

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INTERACTIONS:

Niraparib weakly induces CYP 1A2 *in vitro;* clinical significance is unknown.[2,3]

Niraparib inhibits MATE-1 and -2 and weakly inhibits Breast Cancer Resistance Protein (BCRP), P-glycoprotein (P-gp) and organic cation transporter 1 (OCT1); clinical significance is unknown.[2,3]

Niraparib is a substrate of carboxylesterases (CEs), UDP-glucuronosyltransferases (UGTs), BCRP and P-gp; clinical significance is unknown.[2,3]

SUPPLY AND STORAGE:

Oral: GlaxoSmithKline Inc. supplies niraparib as 100 mg capsules and tablets. Capsules contain lactose and tartrazine. Tablets contain lactose. Store at room temperature.[5]

Additional information:
- capsules and tablets are supplied as unit dose blisters[5]
- capsules and tablets are bioequivalent[11]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral[2,4,12,13]: ***(range 100 – 300 mg) PO once daily***; see tables below

Administer with food or on an empty stomach.
Administration at bedtime may help reduce nausea.

For **advanced disease:** starting dose is based on weight and platelet count:

Platelet ($\times 10^9$/L)		Weight	Starting Dose (PO once daily)
<150	**or**	<77 kg	200 mg
≥150	**and**	≥77 kg	300 mg

For **recurrent disease:** starting dose has a consideration for weight:

Weight	Starting Dose (PO once daily)
<58 kg	consider starting dose of 200 mg
≥58 kg	300 mg

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

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Dosage in renal failure:	creatinine clearance ≥30 mL/min: no adjustment required[2,4] creatinine clearance <30 mL/min: no information found calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild hepatic impairment (Child-Pugh class A): no adjustment required[2,4] moderate hepatic impairment (Child-Pugh class B): reduce starting dose to 200 mg PO once daily; monitor for toxicity[14] severe hepatic impairment (Child-Pugh class C): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy not established[2]

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