# Niraparix
Niraparib

## COMPOSITION

***Niraparix Capsule:*** Each capsule contains Niraparib Tosylate Monohydrate INN equivalent to Niraparib 100 mg

**THERAPEUTIC CLASS:** Anti Cancer

## CLINICAL PHARMACOLOGY

***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.

***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)

***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.

***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 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, Cmax, 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 (±SD) apparent volume of distribution (Vd/F) was 1220 (±1114) L. In a population pharmacokinetic analysis, the Vd/F of Niraparib was 1074 L in cancer patients.

***Elimination***

Following multiple daily doses of 300 mg Niraparib, the mean half-life (t1/2) 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.

## INDICATIONS AND USAGE

Niraparib 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.

## DOSAGE AND ADMINISTRATION

***Recommended Dosage***

The recommended dose of Niraparib as monotherapy is 300 mg (three 100 mg capsules) taken orally once daily. Instruct patients to take their dose of Niraparib at approximately the same time each day. Each capsule should be swallowed whole. Niraparib may be taken with or without food. Bedtime administration may be a potential method for managing nausea. Patients should start treatment with Niraparib no later than 8 weeks after their most recent platinum containing regimen. Niraparib treatment should be continued until disease progression or unacceptable toxicity. In the case of a missed dose of Niraparib, instruct patients to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of Niraparib, an additional dose should not be taken.

***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.

Table: Recommended dose modifications for adverse reactions

| 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 Niraparib.

Table 2: Dose modifications for non-hematologic adverse reactions

| | |
|---|---|
| Non-hematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment | Withhold Niraparib for a maximum of 28 days or until resolution of adverse reaction.<br>Resume Niraparib 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 Niraparib 100 mg/day | Discontinue medication. |

*CTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose modifications for hematologic adverse reactions

| | |
|---|---|
| Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment and periodically after this time. | |
| Platelet count <100,000/µL | First occurrence:<br>Withhold Niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL.<br>Resume Niraparib at same or reduced dose per Table 1. If platelet count is <75,000/µL, resume at a reduced dose. |
| | Second occurrence:<br>Withhold Niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume Niraparib at a reduced dose per Table 1. Discontinue Niraparib 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<br>Hemoglobin <8 g/dL | Withhold Niraparib 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 Niraparib at a reduced dose per Table 1. Discontinue Niraparib 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 | 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 Niraparib at a reduced dose. |

*If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue Niraparib.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

***Myelodysplastic Syndrome/Acute Myeloid Leukemia***

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received Niraparib. In Trial 1 (NOVA), MDS/AML occurred in 5 out of 367 (1.4%) of patients who received Niraparib 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 Niraparib in clinical studies.

The duration of Niraparib 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 Niraparib if MDS/AML is confirmed.

***Bone Marrow Suppression***

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with Niraparib. Grade ≥3 thrombocytopenia, anemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving Niraparib. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

Do not start Niraparib until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ 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 Niraparib, and refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics.

***Cardiovascular Effects***

Hypertension and hypertensive crisis have been reported in patients treated with Niraparib. Grade 3-4 hypertension occurred in 9% of Niraparib 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 Niraparib. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Medically manage hypertension with antihypertensive medications and adjustment of the Niraparib dose.

***Embryo-Fetal Toxicity***

Based on its mechanism of action, Niraparib can cause fetal harm when administered to a pregnant Woman. Niraparib 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). 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 Niraparib.

## SIDE EFFECTS

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

## USE IN SPECIFIC POPULATIONS

***Pregnancy***

Based on its mechanism of action, Niraparib can cause fetal harm when administered to pregnant women. There are no data regarding the use of Niraparib in pregnant women to inform the drug-associated risk. Niraparib 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). 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.

***Lactation***

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 Niraparib, advise a lactating woman not to breastfeed during treatment with Niraparib and for 1 month after receiving the final dose.

Females and Males of Reproductive Potential

***Pregnancy Testing***

Niraparib can cause fetal harm when administered to a pregnant woman.

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

***Contraception***

***Females***

Niraparib can cause fetal harm when administered to a pregnant woman.

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

***Infertility***

***Males***

Based on animal studies, Niraparib may impair fertility in males of reproductive potential

***Pediatric Use***

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

***Geriatric Use***

In Clinical Trial, 35% of patients were aged ≥65 years and 8% were aged ≥75 years. No overall differences in safety and effectiveness of Niraparib were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

***Renal Impairment***

No dose adjustment is necessary for patients with mild ($CL_{cr}$:60 to 89 mL/min) to moderate ($CL_{cr}$: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 Niraparib in patients with severe renal impairment or end stage renal disease undergoing hemodialysis is unknown.

Hepatic Impairment The safety of Niraparib in patients with moderate to severe hepatic impairment is unknown.

***Drug Interaction Studies***

No formal drug interaction studies have been performed with Niraparib.

*In Vitro Studies*

*Inhibition of CYPs:* Neither Niraparib nor the major primary metabolite M1 is an inhibitor of CYPA2, 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 UDPglucuronosyltransferases (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 BESP. 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 BESP. 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).

## OVERDOSAGE

There is no specific treatment in the event of Niraparib 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.

## PHARMACEUTICAL INFORMATIONS

**Storage condition**

Store below $30^0$C and dry place, away from light and moisture. Keep out of the reach of children.

***Presentation & Packaging***

***Niraparix Capsule:*** Each Commercial box contains 90 capsules in a HDPE pot.

Only for Export

Manufactured By
**Beacon Pharmaceuticals Limited**
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

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