Niranib

Niraparib 100 mg

Everest

COMPOSITION

NIRANIB Capsule: Each capsule contains Niraparib Tosylate Monohydrate INN equivalent to Niraparib 100 mg.

INDICATIONS AND USAGE

NIRANIB 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

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 1, 2 and 3.

Table 1: 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 NIRANIB for a maximum of 28 days or until resolution of adverse reaction. • Resume NIRANIB 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 NIRANIB 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: • Withhold NIRANIB for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume NIRANIB at same or reduced dose per Table 1. • If platelet count is <75,000/µL, resume at a reduced dose.
	Second occurrence: • Withhold NIRANIB for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume NIRANIB at a reduced dose per Table 1. • Discontinue NIRANIB 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	• Withhold NIRANIB 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 NIRANIB at a reduced dose per Table 1. • Discontinue NIRANIB 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 NIRANIB at a reduced dose.

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

Patients with low body weight

Approximately 25% of patients in the NOVA study 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.

Elderly

No dose adjustment is necessary for elderly patients (≥ 65 years). There are limited clinical data in patients aged 75 or over.

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients.

Hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment; use with caution in these patients.

Patients with ECOG performance status 2 to 4

Clinical data are not available in patients with ECOG performance status 2 to 4.

Paediatric population

The safety and efficacy of niraparib in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Oral use. The capsules should be swallowed whole with water. The capsules should not be chewed or crushed. Niraparib can be taken without regard to meals.

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients & breast-feeding.

WARNINGS & PRECAUTIONS

Myelodysplastic syndrome/acute myeloid leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received Niraparib or placebo. In the pivotal Phase 3 international trial (ENGOT-OV16), the incidence of MDS/AML in patients who received niraparib (1.4%) was similar to that in patients who received placebo (1.1%). 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. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

If MDS and/or AML are confirmed while on treatment with Niraparib, treatment should be discontinued and the patient treated appropriately.

Hypertension including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of Niraparib. Pre-existing hypertension should be adequately controlled before starting Niraparib treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with Niraparib.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Niraparib dose, if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on Niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without Niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Pregnancy/contraception

Niraparib should not be used during pregnancy or in women of childbearing potential not willing to use reliable contraception during therapy and for 1 month after receiving the last dose of Niraparib. A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Lactose

Niraparib hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tartrazine (E 102)

This medicinal product contains tartrazine (E 102), which may cause allergic reactions.

SIDE EFFECTS

In the pivotal ENGOT-OV16 study, adverse reactions (ADRs) occurring ≥ 10% of patients receiving Niraparib monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.

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

DRUG INTERACTIONS

Pharmacodynamic interactions

The combination of Niraparib with vaccines or immunosuppressant agents has not been studied.

The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Pharmacokinetic interactions

Effect of other medicinal products on Niraparib

Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)

Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*. No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit (e.g. itraconazole, ritonavir, and clarithromycin) or induce CYP enzymes (e.g. rifampin, carbamazepine and phenytoin).

Niraparib as a substrate of efflux transporters (P-gp, BCRP and MATE1/2)

Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit P-gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

Niraparib is not a substrate of bile salt export pump (BSEP). The major primary metabolite M1 is not a substrate of P-gp, BCRP or BSEP. Niraparib is not a substrate of MATE 1 or 2, while M1 is a substrate of both.

Niraparib as a substrate of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither Niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1). No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit OATP1B1 or 1B3 (e.g. gemfibrozil, ritonavir) or OCT1 (e.g. dolutegravir) uptake transporters.

Niraparib as a substrate of renal uptake transporters (OAT1, OAT3 and OCT2)

Neither Niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3) and organic cation transporter 2 (OCT2). No dose adjustment for Niraparib is required when administered concomitantly with medicinal products known to inhibit OAT1 (e.g. probenecid) or OAT3 (e.g. probenecid, diclofenac) or OCT2 (e.g. cimetidine, quinidine) uptake transporters.

Effect of niraparib on other medicinal products
Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)

Neither Niraparib nor M1 is an inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.

Even though inhibition of CYP3A4 in the liver is not expected, 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 the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine and halofantrine).

Induction of CYPs (CYP1A2 and CYP3A4)
Neither Niraparib nor M1 is a CYP3A4 inducer *in vitro*. *In vitro*, Niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect would not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline and ropinirole).

Inhibition of efflux transporters (P-gp, BCRP, BSEP, and MATE1/2)
Niraparib is not an inhibitor of BSEP. *In vitro*, Niraparib inhibits P-gp very weakly and BCRP with an IC50 = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters although unlikely, cannot be excluded. Caution is then recommended when Niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin and methotrexate).

Niraparib is an inhibitor of MATE1 and -2 with IC50 of 0.18 µM and ≤ 0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g. metformin) cannot be excluded.

The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, BSEP or MATE1/2.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)
Neither Niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1) or 1B3 (OATP1B3).

In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC50 = 34.4 µM. Caution is recommended when Niraparib is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)
Neither Niraparib nor M1 inhibits organic anion transporter 1 (OAT1), 3 (OAT3) and organic cation transporter 2 (OCT2).

All clinical studies have only been performed in adults.

USE IN SPECIFIC POPULATION
Women of childbearing potential/contraception in females
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 Niraparib.

Pregnancy
There are no or limited amount of data from the use of Niraparib in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted. However, based on its mechanism of action, niraparib could cause embryonic or foetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. Niraparib should not be used during pregnancy.

Breast-feeding
It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of Niraparib and for 1 month after receiving the last dose.

Fertility
There are no clinical data on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs.

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

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 Niraparib were observed between these patients and younger patients but greater sensitivity of some older individuals cannot be ruled out.

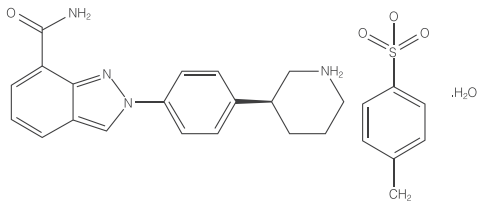
Renal Impairment
No dose adjustment is necessary for patients with mild (CLcr:60 to 89mL/min) to moderate (CLcr:30 to 59mL/min) renal impairment. The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. The safety of NIRAPARIB in patients with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

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

OVERDOSE
There is no specific treatment in the event of Niraparib overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

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-indazole7-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 pK_a of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

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) [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.

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.

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.

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.

NONCLINICAL TOXICOLOGY
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 (AUC0-24hr) at the recommended dose of 300 mg daily. There was a trend toward reversibility of these findings 4 weeks after dosing was stopped.

PHARMACEUTICAL INFORMATION
Storage Conditions
Store in a cool and dry place. Do not store above 30°C. Do not take NIRANIB if it is suspected of having been exposed to temperatures greater than 40°C or 104° F.

Keep NIRANIB out of the reach and sight of children.

HOW SUPPLIED
NIRANIB Capsule: Each HDPE container contains 30 Capsules, each of which contains Niraparib 100 mg.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com
1901000020