Olanib
Olaparib 50 mg

Everest

COMPOSITION
Olanib Capsule**:** Each hard gelatin capsule contains Olaparib INN 50 mg.

INDICATIONS AND USAGE
Olaparib (**Olanib**) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germ line BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

DOSAGE AND ADMINISTRATION
The recommended dose of Olaparib (**Olanib**) is 400 mg (eight 50 mg capsules) taken twice daily, for a total daily dose of 800 mg. Continue treatment until disease progression or unacceptable toxicity.
If a patient misses a dose of Olaparib (**Olanib**), instruct patient to take their next dose at its scheduled time.
Swallow capsule whole. Do not chew, dissolve, or open capsule. Do not take capsules which appear deformed or show evidence of leakage.

Dose Adjustments for Adverse Reactions
To manage adverse reactions, consider dose interruption of treatment or dose reduction.
The recommended dose reduction is to 200 mg (four 50 mg capsules) taken twice daily, for a total daily dose of 400 mg.
If a further final dose reduction is required, then reduce to 100 mg (two 50 mg capsules) taken twice daily, for a total daily dose of 200 mg.

Dose Modifications for Use with CYP3A Inhibitors
Avoid concomitant use of strong and moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If the inhibitor cannot be avoided, reduce the Olaparib (**Olanib**) dose to 150 mg (three 50 mg capsules) taken twice daily for a strong CYP3A inhibitor or 200 mg (four 50 mg capsules) taken twice daily for a moderate CYP3A inhibitor.

Dose Modifications for Patients with Renal Impairment
Patients with mild renal impairment (CLcr 51-80 mL/min as estimated by Cockcroft-Gault) do not require an adjustment in Olaparib (**Olanib**) dosing. In patients with moderate renal impairment (CLcr 31-50 mL/min) the recommended dose reduction is to 300 mg (six 50 mg capsules) taken twice daily, for a total daily dose of 600 mg. The pharmacokinetics of Olaparib (**Olanib**) have not been evaluated in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

CONTRAINDICATIONS
Hypersensitivity to Olaparib or to any of the excipients.

WARNINGS AND PRECAUTIONS
Myelodysplastic Syndrome/Acute Myeloid Leukemia
Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) have been confirmed in 6 out of 298 (2%) patients enrolled in a single arm trial of Olaparib monotherapy, in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced cancers. In a randomized placebo controlled trial, MDS/AML occurred in 3 out of 136 (2%) patients with advanced ovarian cancer treated with Olaparib. Overall, MDS/AML were reported in <1% patients treated with Olaparib in clinical studies. The majority of MDS/AML reports were fatal, and the duration of therapy with Olaparib in patients who developed secondary MDS/ cancer- therapy related AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Some of these patients also had a history of previous cancer or of bone marrow dysplasia.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Olaparib (**Olanib**) until patients have recovered from hematological toxicity caused by previous chemotherapy (CTCAE Grade 1). For prolonged hematological toxicities, interrupt Olaparib (**Olanib**) and monitor blood counts weekly until recovery. If the levels have not recovered to CTCAE Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Olaparib (**Olanib**).

Pneumonitis
Pneumonitis, including fatal cases, occurred in <1% of patients treated with Olaparib (**Olanib**). If patients present with new or worsening respiratory symptoms such as dyspnea, fever, cough, wheezing, or a radiological abnormality occurs, interrupt treatment with Olaparib (**Olanib**) and initiate prompt investigation. If pneumonitis is confirmed, discontinue Olaparib (**Olanib**).

Embryo-Fetal Toxicity
Olaparib (**Olanib**) can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Olaparib (**Olanib**) was teratogenic and caused embryo-fetal toxicity in rats at exposures below those in patients receiving the recommended human dose of 400 mg twice daily. If the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.
Advise females of reproductive potential to avoid becoming pregnant while taking Olaparib (**Olanib**). If contraceptive methods are being considered, use effective contraception during treatment and for at least one month after receiving the last dose of Olaparib (**Olanib**).

ADVERSE REACTIONS
Most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/ URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and abdominal pain/discomfort.
Most common laboratory abnormalities (≥25%) were increase in creatinine, mean corpuscular volume elevation, decrease in hemoglobin, decrease in lymphocytes, decrease in leucocytes, decrease in absolute neutrophil count, and decrease in platelets.

DRUG INTERACTIONS
Anticancer Agents
Clinical studies of Olaparib in combination with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Drugs that may Increase Olaparib Plasma Concentrations
Olaparib (**Olanib**) is primarily metabolized by CYP3A. Avoid concomitant use of strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir/ritinovir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil). If the strong or moderate CYP3A inhibitors must be co-administered, reduce the dose of Olaparib (**Olanib**). **Avoid grapefruit and Seville oranges during Olaparib (Olanib) treatment.**

Drugs that may Decrease Olaparib (Olanib) Plasma Concentrations
Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy of Olaparib (**Olanib**).

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy category is D. Olaparib (**Olanib**) can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Olaparib (**Olanib**) was teratogenic and caused embryo-fetal toxicity in rats at exposures below those in patients receiving the recommended human dose of 400 mg twice daily. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

Nursing Mothers
It is not known whether Olaparib (**Olanib**) is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Olaparib (**Olanib**), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Populations With Reproductive Potential
Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Olaparib.
Olaparib (**Olanib**) can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use highly effective contraception during treatment with Olaparib (**Olanib**) and for at least 6 months following the last dose.

Pediatric Use
The safety and efficacy of Olaparib (**Olanib**) has not been established in pediatric patients.

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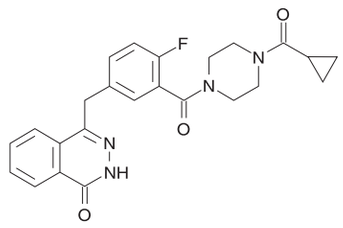
Geriatric Use
In clinical studies it was found that the safety profile was similar irrespective of age with the exception of AEs of CTCAE ≥3 which were reported more frequently in patients aged ≥65 years (53.4%) than those <65 years (43.4%). No individual adverse event or System Organ Class accounted for this observed difference

Hepatic Impairment
No adjustment to the starting dose is required in patients with mild hepatic impairment. A 1.2-fold increase in mean exposure (AUC) of Olaparib was observed in patients with mild hepatic impairment (based on Child-Pugh classification A) compared to patients with normal hepatic function. There are no data in patients with moderate or severe hepatic impairment.

Renal Impairment
No dose adjustment to the starting dose is required in patients with mild renal impairment, but patients should be monitored closely for toxicity. For patients with moderate renal impairment, reduce the dose of Olaparib (**Olanib**) to 300 mg twice daily (please see Dosage and Administration). There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min).

OVERDOSAGE
There is no specific treatment in the event of Olaparib (**Olanib**) 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
Olaparib is an inhibitor of the mammalian polyadenosine 5'-diphosphoribose polymerase (PARP) enzyme.
The chemical name is 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one and it has the following chemical structure:



The empirical molecular formula for Olaparib is $C_{24}H_{23}FN_4O_3$ and the relative molecular mass is 434.46.
Olaparib is a crystalline solid, is non-chiral and shows pH-independent low solubility of approximately 0.1 mg/mL across the physiological pH range.
Olanib (Olaparib) is available in 50 mg capsules for oral administration. Each capsule contains Olaparib as the active ingredient and required pharmaceutical excipients.

CLINICAL PHARMACOLOGY
Mechanism of Action
Olaparib (**Olanib**) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines *in vitro* and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with Olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. *In vitro* studies have shown that Olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.

Pharmacokinetics
Absorption
Following oral administration of Olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple dosing there is no marked accumulation (accumulation ratio of 1.4 – 1.5 for twice daily dosing), with steady state exposures achieved within 3 to 4 days.

Distribution
Olaparib had a mean (± standard deviation) apparent volume of distribution at steady state of 167 ± 196 L after a single 400 mg dose of Olaparib. The *in vitro* protein binding of Olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is approximately 82%.

Metabolism
In vitro, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of Olaparib. The majority of the metabolism is attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulfate conjugation.

Excretion
A mean (± standard deviation) terminal plasma half-life of 11.9 ± 4.8 hours and apparent plasma clearance of 8.6 ± 7.1L/h were observed after a single 400 mg dose of Olaparib.

Drug Interactions
In vitro studies have shown that Olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Simulations suggested that Olaparib may not affect the exposure of a CYP3A substrate in humans. It cannot be excluded that Olaparib may induce CYP2C9 and CYP2C19. *In vitro* studies also indicated that Olaparib is a substrate of P-gp and an inhibitor of P-gp (MDR1), BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown. The potential for Olaparib to induce P-gp has not been evaluated.

Pharmacokinetics in Specific Populations
Hepatic Impairment
In a hepatic impairment trial, the mean AUC increased by 15% and the mean Cmax by 13% when Olaparib was dosed in patients with mild hepatic impairment (Child-Pugh classification A; N=9) compared with patients with normal hepatic function (N=13). Mild hepatic impairment had no effect on the protein binding of Olaparib and therefore total plasma exposure was representative of free drug. There are no data in patients with moderate or severe hepatic impairment.

Renal Impairment
In a dedicated renal impairment trial, the mean AUC and C_{max} of Olaparib both increased by 1.2-fold, when Olaparib was dosed in patients with mild renal impairment (CLcr = 51-80 mL/min defined by the Cockcroft-Gault equation; N=13) and by 1.4- and 1.3-fold, respectively, when Olaparib was dosed in patients with moderate renal impairment (CLcr = 31-50 mL/min; N=13), compared to those with normal renal function (CLcr ≥81 mL/min; N=12). There was no evidence of a relationship between the extent of plasma protein binding of Olaparib and creatinine clearance. There is no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤ 30 mL/min).

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been conducted with Olaparib.
Olaparib was clastogenic in an *in vitro* chromosomal aberration assay in mammalian CHO cells and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of Olaparib and indicates potential for genotoxicity in humans. Olaparib was not mutagenic in a bacterial reverse mutation (Ames) test.

In a fertility study, female rats received oral Olaparib at doses of 0.05, 0.5, and 15 mg/kg/day for at least 14 days before mating through the first week of pregnancy. There were no adverse effects on mating and fertility rates at doses up to 15 mg/kg/day (maternal systemic exposures approximately 11% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In a male fertility study, Olaparib had no effect on mating and fertility in rats at oral doses up to 40 mg/kg/day following at least 70 days of Olaparib treatment (with systemic exposures of approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

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

Keep **Olanib** out of the reach and sight of children.

HOW SUPPLIED
Olanib Capsule: Each HDPE container contains 112 Capsules, each of which contains Olaparib INN 50 mg.

Manufactured By
Everest Pharmaceuticals Ltd.
Narayangonj, Bangladesh
www.everestpharmabd.com