PRESCRIBING INFORMATION

℞ Olaparib Tablets

OLABIR™

Each film coated tablet contains:		Each film coated tablet contains:	
Olaparib	100 mg	Olaparib	150 mg
Excipients	qs	Excipients	qs
Colours : Yellow Oxide of Iron, Titanium Dioxide IP		Colours : Black Oxide of Iron, Yellow Oxide of Iron, Titanium Dioxide IP	

DOSAGE FORM : Film Coated Tablets For Oral Use Only

PHARMACOLOGICAL PROPERTIES:

Mechanism of action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription 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 and non-BRCA proteins involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage and cancer cell death.

Pharmacokinetics

Absorption

Following oral administration of olaparib, absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing. An AUC mean accumulation ratio of 1.8 is observed at steady state following multiple dosing of 300 mg tablets twice daily.

Systemic exposure (single dose AUC) to olaparib increases approximately proportionally with doses over the dose range of 25 mg to 450 mg, Cmax increased slightly less than proportionally for the same dose range.

Co-administration of a high fat meal with olaparib slowed the rate (tmax delayed by 2.5 hours) of absorption, but did not significantly alter the extent of olaparib absorption (mean AUC increased by approximately 8%).

Distribution

Olaparib had a mean (± standard deviation) apparent volume of distribution of 158 ± 136 L after a single 300 mg dose of olaparib. The in vitro protein binding of olaparib is approximately 82%.

Metabolism

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib.

Following oral dosing of 14C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%). It was extensively metabolized with unchanged drug accounting for 15% and 6% of radioactivity in urine and faeces, respectively. 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 14.9 ± 8.2 hours and apparent plasma
clearance of 7.4 ± 3.9 L/h were observed after a single 300 mg dose of olaparib.

Following a single dose of 14C-olaparib, 86% of the dosed radioactivity was recovered within a 7-day collection period, 44% via the urine and 42% via the feces. The majority of the material was excreted as metabolites.

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 there for total plasma exposure was representative of free drug. There are no data in patients with moderate or severe hepatic impairment.

Renal Impairment

In a renal impairment trial, the mean AUC increased by 24% and Cmax by 15%, 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 44% and 26%, 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 are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤ 30 mL/min).

If you have been told by your doctor that you have heart problems such as heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, bypass surgery, peripheral arterial disease (poor circulation in legs or feet due to narrow or blocked arteries), or any kind of stroke (including mini-stroke, transient Ischaemic attack (TIA)). Olaparib may slightly increase your risk of heart attack and stroke and this is why it should not be used in those who have already had heart problems or stroke.

If you think any of these are relevant to you, do not take the tablets until you have consulted your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking Olaparib if:

You have a history of bleeding or ulcers in your stomach or intestines

You are taking acetylsalicylic acid (even at low dose for heart protective purposes) or other NSAIDs

You are dehydrated, for example by a prolonged bout of vomiting or diarrhoea

You have swelling due to fluid retention

You have a history of high blood pressure. Olaparib can increase blood pressure in some people, especially in high doses, and your doctor will want to check your blood pressure from time to time

You have any other problems with your heart, liver or kidneys

You are being treated for an infection. Olaparib can mask or hide a fever,

THERAPEUTIC INDICATIONS

Ovarian Cancer

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.

Breast Cancer

In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment.

DOSAGE AND ADMINISTRATION:

The recommended dose of Olaparib Tablets is 300 mg (two 150 mg tablets) taken orally twice daily, with or without food, for a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Continue treatment until disease progression or unacceptable toxicity.

If a patient misses a dose of Olaparib Tablets, instruct patient to take their next dose at its scheduled time.

Swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

Dose Adjustments for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction.

The recommended dose reduction is 250 mg (one 150 mg tablet and one 100 mg tablet) taken twice daily, for a total daily dose of 500 mg.

If a further dose reduction is required, then reduce to 200 mg (two 100 mg tablets) taken twice daily, for a total daily dose of 400 mg.

Dose Modifications for Use with CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, reduce the Olaparib Tablets dose to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, reduce the Olaparib Tablets dose to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg.

Dose Modifications for Patients with Renal Impairment

Patients with mild renal impairment (CLcr 51-80 mL/min as estimated by Cockcroft-Gault equation) do not require an adjustment in Lynparza dosing. In patients with moderate renal impairment (CLcr 31-50 ml/min) the recommended dose reduction is to 200 mg (two 100 mg tablets) twice daily, for a total daily dose of 400 mg. The pharmacokinetics of Olaparib have not been evaluated in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min)

Contraindications

Hypersensitivity to the active substance or to any of the excipients used in formulation.

Special warnings and precautions for use

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Olaparib Tablets monotherapy in clinical trials, including long-term follow up, was < 6 months to > 2 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Some of these patients also had a history of more than one primary malignancy or of bone marrow dysplasia. Do not start Olaparib Tablets until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Olaparib Tablets and monitor blood counts weekly until recovery. If the levels have not recovered to 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 Tablets.

Pneumonitis

Pneumonitis, including fatal cases, occurred in <1% of patients treated with Olaparib Tablets. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological
abnormality occurs, interrupt Olaparib Tablets treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Olaparib Tablets treatment and treat the patient appropriately.

Embryo-Fetal Toxicity

Olaparib Tablets. can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily.

Apprise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Olaparib Tablets.

Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Olaparib Tablets.

Interaction with other medicinal products and other forms of interaction

Anticancer Agents

Clinical studies of Lynparza 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 is primarily metabolized by CYP3A. In patients (n=57), co-administration of itraconazole, a

strong CYP3A inhibitor, increased AUC of olaparib by 170%. A moderate CYP3A inhibitor,

fluconazole, is predicted to increase the AUC of olaparib by 121%.

Avoid concomitant use of strong CYP3A inhibitors such as itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir or moderate CYPA inhibitors such as amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil. If the strong or moderate CYP3A inhibitors must be coadministered, reduce the dose of Olaparib Tablets.

Avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during Olaparib Tablets. treatment since they are CYP3A inhibitors

Drugs That May Decrease Olaparib Plasma Concentrations

In patients (n=22), co-administration of rifampicin, a strong CYP3A inducer, decreased AUC of olaparib by 87%. A moderate CYP3A inducer, efavirenz, is predicted to decrease the AUC of olaparib by approximately 60%.

Avoid concomitant use of strong CYP3A inducers such as phenytoin, rifampicin, carbamazepine, and St. John's Wort or moderate CYP3A4 inducers such as bosentan, efavirenz, etravirine, modafinil, and

nafcillin. If a moderate CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of Olaparib Tablets.

Pregnancy and Lactation

Pregnancy

Based on findings in animals and its mechanism of action, Olaparib Tablets can cause fetal harm when administered to a pregnant woman. There are no available data on Olaparib Tablets use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

Lactation

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Olaparib Tablets, advise a lactating woman not to breastfeed during treatment with Olaparib Tablets and for one month after receiving the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Olaparib Tablets.

Contraception

Females

Olaparib Tablets can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with Olaparib Tablets and for at least 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Olaparib Tablets. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Olaparib Tablets.

Effects on ability to drive and use machines

Olaparib Tablets has moderate influence on the ability to drive and use machines. Patients who take Olaparib

Tablets may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines

Undesirable effects

Maintenance Treatment of Recurrent Ovarian Cancer

SOLO-2

The safety of Olaparib Tablets for the maintenance treatment of patients with platinum sensitive gBRCAm ovarian cancer was investigated in SOLO-2. This study was a placebo-controlled, double-blind study in which 294 patients received either Olaparib Tablets 300 mg (2 x 150 mg tablets) twice daily (n=195) or placebo tablets twice daily (n=99) until disease progression or unacceptable toxicity. The median duration of study treatment was 19.4 months for patients who received Olaparib Tablets and 5.6 months for patients who received placebo. Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Olaparib Tablets and 18% of those receiving placebo; dose reductions due to an adverse reaction occurred in 27% of Olaparib Tablets patients and 3% of placebo patients. The most frequent adverse reactions leading to dose interruption or reduction of Olaparib Tablets were anemia (22%), neutropenia (9%), and fatigue/asthenia (8%). Discontinuation occurred in 11% of Olaparib Tablets patients and 2% in placebo patients.

In addition, the adverse reactions observed in SOLO-2 that occurred in <20% of patients receiving Olaparib Tablets were neutropenia, rash, cough, dyspepsia, leukopenia, hypomagnesemia, dizziness, thrombocytopenia, increase in creatinine, lymphopenia and edema.

Treatment of gBRCAm HER2-negative Metastatic Breast Cancer

The safety of Olaparib tablets as monotherapy was also evaluated in gBRCAm patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in Olaparib. This study was a randomized, open-label, multi-center study in which 296 patients received either Olaparib 300 mg twice daily (n=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Olaparib and 3.4 months in patients who received chemotherapy. Dose interruptions due to an adverse reaction of any grade occurred in 35% of patients receiving Olaparib and 28% of those receiving chemotherapy; dose reductions due to an adverse reaction occurred in 25% of Olaparib patients and 31% of chemotherapy patients. Discontinuation occurred in 5% of Olaparib patients and 8% in chemotherapy patients.

In addition, adverse reactions in that occurred in <20% of patients receiving Lynparza were cough, decreased appetite, thrombocytopenia, dysgeusia, lymphopenia, dizziness, dyspepsia, stomatitis, upper abdominal pain, rash, increase in serum creatinine and dermatitis

Overdose

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

HOW SUPPLIED/STORAGE AND HANDLING

Presentation:30,60 & 120 tablets are supplied in bottles

Shelf life

24 Months from the date of manufacturing.

Incompatibility

Not applicable

Storage Condition

Storage: Store below 30^{0}C. Protected from light & moisture.

Made in India by:
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