Parib-150

Olaparib INN

DRUG INTERNATIONAL LTD.

COMPOSITION

Parib-150: Each tablet contains Olaparib INN 150mg.

CLINICAL PHARMACOLOGY

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 feces, 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.

INDICATIONS

First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer:

Olaparib is indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAmor sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Olaparib.

Maintenance Treatment of Recurrent Ovarian Cancer:

Olaparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

Advanced gBRCA-mutated Ovarian Cancer After 3 or More Lines of Chemotherapy:

Olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Olaparib.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer:

Olaparib is indicated in patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have 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 therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Olaparib.

DOSAGE AND ADMINISTRATION

Patient Selection: First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer: Select patients with advanced ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy for maintenance treatment with Olaparib based on the presence of deleterious or suspected deleterious gBRCAmor sBRCAm.

Advanced gBRCAm Ovarian Cancer: Select patients with advanced ovarian cancer with Olaparib based on the presence of deleterious or suspected deleterious gBRCA-mutation.

gBRCAm HER2-negative Metastatic Breast Cancer: Select patients for the treatment of HER2-negative metastatic breast cancer with Lynparza based on the presence of deleterious or suspected deleterious gBRCA-mutation.

Recommended Dosing: The recommended dose of Olaparib 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.

If a patient misses a dose of Olaparib, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

First-Line Maintenance Treatment of BRCA-mutated Advanced Ovarian Cancer: Continue treatment until disease progression, unacceptable toxicity, or completion of 2 years of treatment. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating healthcare provider can derive further benefit from continuous treatment, can be treated beyond 2 years.

Maintenance Treatment of Recurrent Ovarian Cancer: Continue treatment until disease progression or unacceptable toxicity.

Advanced gBRCA-mutated Ovarian Cancer: Continue treatment until disease progression or unacceptable toxicity.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer: Continue treatment until disease progression or unacceptable toxicity.

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 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 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 Olaparib 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).

Or as directed by the registered physician.

ADVERSE EFFECTS

Myelodysplastic Syndrome/Acute Myeloid Leukemia, Pneumonitis.

CONTRAINDICATIONS

It is contraindicated in patients with known hypersensitivity to Olaparib or to any component of the formulation.

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 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, and telaprevir. Avoid use of moderate CYP3A inhibitors such as amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, and verapamil. If the strong or moderate CYP3A inhibitors must be co-administered, reduce the dose of Olaparib. Avoid grapefruit, grapefruit juice, Seville oranges and Seville orange juice during Olaparib 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 50%. Avoid concomitant use of strong CYP3A inducers such as phenytoin, rifampicin, carbamazepine, and St. John's Wort. Avoid concomitant use of moderate CYP3A4 inducers such as bosentan, efavirenz, etravirine, modafinil, and nafcillin. If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy of Olaparib.

PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia: Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Olaparib monotherapy in clinical trials, including long-term follow up, was <1.5% (21/1680) and the majority of events had a fatal outcome. Of these, 19/21 patients had a documented BRCA mutation, 1 patient had gBRCA wildtype and in 1 patient the BRCA mutation status was unknown. Additional cases of MDS/AML have been documented in patients treated with Olaparib in combination studies. 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 received 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 bone marrow dysplasia.

Do not start Olaparib 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 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.

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

Pediatric Use: The safety and efficacy of Olaparib have not been established in pediatric patients.

Use in Pregnancy: Based on mechanism of action Olaparib can cause fetal harm when administered to a pregnant woman. There are no available data on Olaparib use in pregnant women to inform the drug associated risk. Pregnant women should be apprised of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

Use in Lactation: Because of the potential for serious adverse reactions in the breastfed infants from Olaparib, lactating woman should be advised not to breastfeed during treatment with Olaparib and for one month after receiving the last dose.

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 symptomatically.

PHARMACEUTICAL INFORMATION

Storage: Store below 30°C in a dry place. Keep out of the reach of children.

Packing: Parib-150: Each container contains 120 tablets in a box.