Olaparix 50

Olaparib INN

COMPOSITION

Olaparix 50 Capsule: Each capsule contains Olaparib INN 50 mg.

THERAPEUTIC CLASS: Anti cancer

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 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:

Olaparib is available as a tablet and capsule formulation. The oral bioavailability of the tablet formulation is higher than the capsule formulation.

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.

Limited data suggest that the systemic exposure (AUC) of Olaparib increases less than proportionally with dose over the dose range of 100 to 400 mg, but the PK data were variable across trials.

Co-administration with a high fat meal slowed the rate (T_{max} delayed by 2 hours) of absorption, but did not significantly alter the extent of Olaparib absorption (mean AUC increased by approximately 20%).

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.

Following oral dosing of ^{14}C-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 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.

Following a single dose of ^{14}C-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.

Based on preliminary data from a dedicated renal impairment trial, the mean AUC and C_{max} of Olaparib increased by 1.5- and 1.2-fold, respectively, when Olaparib was dosed in patients with mild renal impairment (CL_{cr} = 50-80 mL/min; N=14) compared to those with normal renal function (CL_{cr} >80 mL/min; N=8). There are no data in patients with CL_{cr} < 50 mL/min or in patients on dialysis

INDICATIONS

Treatment of gBRCA-mutated advanced ovarian cancer

Olaparib is indicated as monotherapy in patients with deleterious or suspected deleterious germline 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

Important Administration Instructions

Olaparib is also available as Olaparib tablets (100 mg and 150 mg). DO NOT substitute Olaparib tablets (100 mg and 150 mg) with Olaparib capsule (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation .

Recommended Dosing

The recommended dose of Olaparib 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, instruct patients 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 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.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic syndrome/Acute Myeloid Leukemia

(MDS/AML) occurred in patients exposed to Olaparib, and some cases were fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.

Pneumonitis

occurred in patients exposed to Olaparib, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed.

Embryo-Fetal toxicity

Olaparib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy.

SIDE EFFECTS

Olaparib may cause serious side effects, including:

- Bone marrow problems called Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).
- Lung problems (pneumonitis)

The most common side effects of Olaparib are

- nausea or vomiting
- diarrhea
- headache
- changes in the way food tastes
- sore throat or runny nose
- cough
- rash
- tiredness or weakness
- indigestion or heartburn
- loss of appetite
- changes in kidney function blood test
- upper respiratory infection
- pain in the joints, muscles, and back
- pain or discomfort in the stomach area

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category D

Olaparib can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Olaparib 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 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, 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.

Pediatric Use

The safety and efficacy of Olaparib has not been established in pediatric patients.

Geriatric Use

As per clinical studies, the safety profile of Olaparib is similar for Geriatric use in comparison to young adults.

Females of Reproductive Potential

Olaparib can cause fetal harm when administered to a pregnant woman.Advise female patients of reproductive potential to avoid pregnancy while taking Olaparib. If contraceptive methods are being considered, use highly effective contraception during treatment with Olaparib and for at least one month following the last dose of Olaparib. Instruct patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking Olaparib.

Hepatic Impairment

The effect of hepatic impairment on exposure to Olaparib has not been studied.

There are no data in patients with baseline hepatic impairment (serum bilirubin >1.5 X ULN).

Renal Impairment

No dose adjustment to the starting dose is required in patients with CL_{cr} of 50 to 80 mL/min, but patients should be monitored closely for toxicity. There are no data in patients with moderate or severe renal impairment (CL_{cr} <50 mL/min) or patients on dialysis.

DRUG INTERACTIONS

CYP3A Inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors. If the inhibitor cannot be avoided, reduce the dose.

CYP3A Inducers

Avoid concomitant use of strong and moderate CYP3A inducers. If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy

OVERDOSAGE

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 & Conditions

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

Presentation & Packaging

Olaparix 50 Capsule: Each commercial box contains 112 capsules in a HDPE pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

LF28501

Olaparix
Olaparib INN

COMPOSITION

Olaparix 100 Tablet: Each film coated tablet contains Olaparib INN 100 mg.

Olaparix 150 Tablet: Each film coated tablet contains Olaparib INN 150 mg.

THERAPEUTIC CLASS : Anti cancer

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.

Pharmacodynamics

Cardiac Electrophysiology

The effect of Olaparib on cardiac repolarization was assessed in 119 patients following a single dose of 300 mg and in 109 patients following multiple dosing of 300 mg twice daily. No clinically relevant effect of Olaparib on QT interval was observed.

Pharmacokinetics

Olaparib is available as a tablet and capsule formulation. The oral bioavailability of the tablet formulation is higher than the capsule formulation. Population pharmacokinetic analyses have shown that the steady state exposure (AUC) following 300 mg tablet twice daily was 77% higher compared to that following 400 mg capsule twice daily. The Olaparib geometric mean AUC and Cmax following a single 300 mg tablet dose were 42.0 µg*h/mL (n = 204) and 5.8 µg/mL (n = 204), respectively, and the steady state geometric mean AUC and Cmax following 300 mg tablet twice daily were 49.0 µg*h/mL (n = 227) and 7.7 µg/mL (n = 227), respectively. Olaparib showed time-dependent PK that the steady state clearance decreased by 15% after multiple dosing.

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, C_{max} increased slightly less than proportionally for the same dose range.

Co-administration of a high fat meal with Olaparib slowed the rate (t_{max} 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 ^{14}C-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 ^{14}C-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

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

Ovarian cancer

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 (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.

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.

Breast cancer

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.

DOSAGE AND ADMINISTRATION

Important Administration Instructions

Olaparib is also available as Olaparib Capsule(50 mg). DO NOT substitute Olaparib Capsule (50 mg) with Olaparib tablet (100 mg and 150 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation.

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.

Continue treatment until disease progression or unacceptable toxicity.

In case of 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.

If a patient misses a dose of Olaparib, 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 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 (CL_{cr} 51-80 mL/min as estimated by Cockcroft-Gault equation) do not require an adjustment in Olaparib dosing. In patients with moderate renal impairment (CL_{cr} 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 (CL_{cr} ≤30 mL/min).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)

Occurred in <1.5% of patients exposed to Olaparib monotherapy and the majority of events had a fatal outcome. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed.

Pneumonitis

Occurred in <1% of patients exposed to Olaparib, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed.

Embryo-Fetal Toxicity

Olaparib can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception.

SIDE EFFECTS

Olaparib may cause serious side effects, including:

- Bone marrow problems called Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML).
- Lung problems (pneumonitis).

The most common side effects of Olaparib are

- nausea or vomiting
- changes in the way food tastes
- loss of appetite
- mouth sores
- respiratory tract infections
- changes in kidney function blood test
- low number of platelets
- indigestion or heartburn
- low number of red or white blood cells
- tiredness or weakness
- sore throat or runny nose
- diarrhea
- joint, muscle, and back pain
- headache
- constipation

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its 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. 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. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Lactation

Risk Summary

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, advise a lactating woman not to breastfeed during treatment with Olaparib 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.

Contraception

Females

Olaparib can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations. Advise females of reproductive potential to use effective contraception during treatment with Olaparib 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. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Olaparib.

Pediatric Use

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

Geriatric Use

No overall differences in the safety or effectiveness of Olaparib were reported between younger and older patients in clinical studies.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild hepatic impairment. A 15% increase in mean exposure (AUC) 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 adjustment to the starting dose is required in patients with mild renal impairment, but patients should be monitored closely for toxicity. A 24% increase in mean exposure (AUC) was observed in patients with mild renal impairment (CL_{cr} = 51-80 mL/min) compared to patients with normal renal function (CLcr >80 mL/min). A 44% increase in AUC was observed in patients with moderate renal impairment (CL_{cr} = 31-50 mL/min) compared to patients with normal renal function (CL_{cr} >80 mL/min). For patients with moderate renal impairment, reduce the dose of Olaparib to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage disease (CL_{cr} ≤30 mL/min).

DRUG INTERACTIONS

CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors. If the inhibitor cannot be avoided, reduce the Olaparib dose.

CYP3A Inducers

Avoid concomitant use of strong or moderate CYP3A inducers as decreased efficacy can occur.

OVERDOSAGE

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.

PHARMACEUTICAL INFORMATION

Storage & Conditions

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

Presentation & Packaging

Olaparix 100 Tablet: Each commercial box contains 120 film coated tablets in a HDPE pot.

Olaparix 150 Tablet: Each commercial box contains 120 film coated tablets in a HDPE pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited
Dhaka, Bangladesh

LF28401

Width	121 mm	Length	453 mm