HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LYNPARZA safely and effectively. See full prescribing information for LYNPARZA.

LYNPARZA® (olaparib) capsules, for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage (1.1)	10/2017
Dosage and Administration (2.1)	01/2017
Warnings and Precautions (5.1, 5.3)	10/2017

INDICATIONS AND USAGE

Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated 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 Lynparza. (1.1, 2.2)

DOSAGE AND ADMINISTRATION

- To avoid substitution errors and overdose, **do not substitute Lynparza capsules with Lynparza tablets** on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. (2.1)
- Recommended capsule dose is 400 mg taken orally twice daily with or without food. (2.3)
- Continue treatment until disease progression or unacceptable toxicity. (2.3)
- For adverse reactions, consider dose interruption or dose reduction. (2.4)
- For moderate renal impairment (CLcr 31-50 mL/min), reduce dose to 300 mg twice daily. (2.6)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg. (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to Lynparza 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. (5.1)
- Pneumonitis: Occurred in <1% of patients exposed to Lynparza, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed. (5.2)
- Embryo-Fetal Toxicity: Lynparza can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, nasopharyngitis/ upper respiratory tract infection/influenza, diarrhea, arthralgia/myalgia, dysgeusia, headache, dyspepsia, decreased appetite, constipation, and stomatitis. (6.1)
- Most common laboratory abnormalities (≥25%) were decrease in
- hemoglobin, increase in mean corpuscular volume, decrease in lymphocytes, decrease in leukocytes, decrease in absolute neutrophil count, increase in serum creatinine, and decrease in platelets. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A Inhibitors: Avoid concomitant use of strong or moderate CYP3A inhibitors. If the inhibitor cannot be avoided, reduce the dose. (2.3, 7.2)
- CYP3A Inducers: Avoid concomitant use of strong or moderate CYP3A inducers as decreased efficacy can occur. (7.3, 12.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: 10/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Advanced *gBRCA*-mutated Ovarian Cancer after 3 or More Lines of Chemotherapy

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (*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 Lynparza.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Lynparza is also available as 100 mg and 150 mg tablets. **DO NOT substitute Lynparza capsules (50 mg) with Lynparza tablets (100 mg and 150 mg)** on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation *[see Clinical Pharmacology (12.3)]*. Refer to the full prescribing information for Lynparza tablets for specific tablet dosing.

2.2 Patient Selection

Select patients for the treatment of advanced ovarian cancer with Lynparza based on the presence of deleterious or suspected deleterious germline *BRCA*-mutations *[see Indications and Usage (1) and Clinical Studies (14)]*. Information on FDA-approved test for the detection of *BRCA*-mutations is available at http://www.fda.gov/companiondiagnostics.

2.3 Recommended Dosing

The recommended dose of Lynparza is 400 mg (eight 50 mg capsules) taken orally twice daily with or without food, for a total daily dose of 800 mg.

Continue treatment until disease progression or unacceptable toxicity.

If a patient misses a dose of Lynparza, 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 *[see How Supplied/Storage and Handling (16.2)]*.

2.4 Dose Adjustments for Adverse Reactions

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

The recommended dose reduction is 200 mg (four 50 mg capsules) taken twice daily, for a total daily dose of 400 mg.

If a further dose reduction is required, then reduce to 100 mg (two 50 mg capsules) taken twice daily, for a total daily dose of 200 mg.

2.5 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 Lynparza 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 *[see Drug Interactions (7.2)]*.

2.6 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 300 mg (six 50 mg capsules) twice daily, for a total daily dose of 600 mg. The pharmacokinetics of olaparib have not been evaluated in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules (50 mg): white, opaque, marked in black ink with “OLAPARIB 50 mg” on the cap and the AstraZeneca logo on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelodysplastic Syndrome/Acute Myeloid Leukemia

Overall, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) in patients treated with Lynparza 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 Lynparza in combination studies. The duration of therapy with Lynparza 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 Lynparza 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 Lynparza 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 Lynparza.

5.2 Pneumonitis

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

5.3 Embryo-Fetal Toxicity

Lynparza 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 400 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 Lynparza *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1)]*
- Pneumonitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Advanced *gBRCAm* Ovarian Cancer after 3 or More Lines of Chemotherapy

Pooled data

Treatment with Lynparza capsules 400 mg twice daily as monotherapy, was studied in 223 patients (pooled from 6 studies) with g*BRCAm* advanced ovarian cancer who had received 3 or more prior lines of chemotherapy.

Adverse reactions led to dose interruption in 40% of patients, dose reduction in 4% of patients, and discontinuation in 7% of patients. There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. The median exposure to Lynparza in these patients was 5.2 months.

Table 1 presents adverse reactions reported in ≥20% of patients and Table 2 presents laboratory abnormalities that occurred in at least 25% of patients from the pooled studies.

Table 1 Adverse Reactions Reported in ≥20% of Patients with *gBRCA*-Mutated Advanced Ovarian Cancer Receiving Lynparza

Adverse Reaction	3 or more lines of prior chemotherapy	
	Grades 1-4 N=223 %	Grades 3-4 N=223 %
Blood and Lymphatic disorders		
Anemia	34	18
Gastrointestinal disorders		
Decreased appetite	22	1
Nausea	64	3
Vomiting	43	4
Diarrhea	31	1
Dyspepsia	25	0
General disorders		
Fatigue/asthenia	66	8
Infections and infestations		
Nasopharyngitis/URI	26	0
Musculoskeletal and Connective Tissue disorders		
Arthralgia/musculoskeletal pain	21	0
Myalgia	22	0

Table 2 Laboratory Abnormalities Reported in ≥25% Patients in Pooled Data

Laboratory Parameter[a]	3 or more lines of prior chemotherapy	
	Grades 1-4 N=223 %	Grades 3-4 N=223 %
Decrease in hemoglobin	90	15
Decrease in absolute neutrophil count	25	7
Decrease in platelets	30	3
Decrease in lymphocytes	56	17
Mean corpuscular volume elevation	57	-
Increase in creatinine[*]	30	2

[a] Patients were allowed to enter clinical studies with laboratory values of Grade 1.

The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving Lynparza and not included in the table: cough, constipation, dysgeusia, peripheral edema, back pain, dizziness, headache, urinary tract infection, dyspnea, and rash.

The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 223 patients receiving Lynparza and not included in the table: leukopenia, stomatitis, peripheral neuropathy, pyrexia, hypomagnesemia, and venous thrombosis (including pulmonary embolism).

Study 19

The safety of Lynparza capsules as maintenance monotherapy was also evaluated in patients with platinum sensitive ovarian cancer who had received 2 or more previous platinum containing regimens in

Study 19, a randomized, placebo-controlled, double-blind, multi-center study in which 264 patients received Lynparza 400 mg twice daily (N=136) or placebo (N=128). At the time of final analysis, the median duration of exposure was 8.7 months in patients who received Lynparza and 4.6 months in patients who received placebo.

Adverse reactions led to dose interruptions in 35% of those receiving Lynparza and 10% of those receiving placebo; dose reductions in 26% of Lynparza patients and 4% of placebo patients; and discontinuation in 6% of Lynparza patients and 2% in placebo patients.

Table 3 summarizes the adverse reactions that occurred in at least 20% of patients who received Lynparza in Study 19. Table 4 presents the laboratory abnormalities that occurred in at least 25% of patients from Study 19.

Table 3 Adverse Reactions[a] in Study 19 (≥20% of Patients who Received Lynparza)

Adverse Reactions	Lynparza N=136		Placebo N=128	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and Lymphatic disorders				
Anemia[b]	23	7	7	1
Gastrointestinal disorders				
Nausea	71	2	36	0
Vomiting	35	2	14	1
Diarrhea	28	2	25	2
Constipation	22	1	12	0
General disorders				
Fatigue (including asthenia)	63	9	46	3
Infections and infestations				
Respiratory tract infection	22	2	11	0
Metabolism and nutrition disorders				
Decreased appetite	21	0	13	0
Nervous system disorder				
Headache	21	0	13	1

[a] Graded according to NCI CTCAE 4.0.
[b] Represents grouped terms of related terms that reflect the medical concept of the adverse reaction.

In addition, the adverse reactions in Study 19 that occurred in <20% of patients receiving Lynparza were dyspepsia, stomatitis, dysgeusia, dizziness, increase in creatinine, neutropenia, thrombocytopenia, leukopenia, lymphopenia, dyspnea, pyrexia and edema.

Table 4 Laboratory Abnormalities Reported in ≥25% Patients in Study 19

Laboratory parameter[a]	Lynparza N=136		Placebo N=129	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Decrease in hemoglobin	82	8	58	1
Increase in mean corpuscular volume	82	-	51	-
Decrease in leukocytes	58	4	37	2
Decrease in lymphocytes	52	10	32	3
Decrease in absolute neutrophil count	47	7	40	2
Mean corpuscular volume elevation	85	-	44	-
Increase in serum creatinine[b]	45	0	14	0
Decrease in platelets	36	4	18	0

[a] Patients were allowed to enter clinical studies with laboratory values of Grade 1.
[b] Represents the proportion of subjects whose mean corpuscular volume was > ULN.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity (rash/dermatitis)

7 DRUG INTERACTIONS

7.1 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.

7.2 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 Lynparza *[see Dosage and Administration (2.5)]*.

Avoid grapefruit, grapefruit juice, Seville oranges and Seville orange juice during Lynparza treatment since they are CYP3A inhibitors *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

7.3 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 Lynparza *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza 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 400 mg twice daily *[see Data]*. 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. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.3% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital) and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter and umbilical artery. Some findings noted above in the eyes, ribs and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

8.2 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 Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use highly effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

In clinical studies of Lynparza enrolling 482 patients with advanced solid tumors who received Lynparza tablets 300 mg twice daily as monotherapy, 135 (28%) patients were aged ≥65 years. There appeared to be no major difference in the safety profile of patients treated with olaparib aged <65 years versus ≥65 years, nor within the age categories of 65 to 74 years, 75 to 84 years. No patients were aged ≥85 years.

8.6 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 *[see Clinical Pharmacology (12.3)]*.

8.7 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 (CLcr = 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 (CLcr = 31-50 mL/min) compared to patients with normal renal function (CLcr >80 mL/min). For patients with moderate renal impairment, reduce the dose of Lynparza capsules to 300 mg twice daily *[see Dosage and*

Administration (2.6)]. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3)]*.

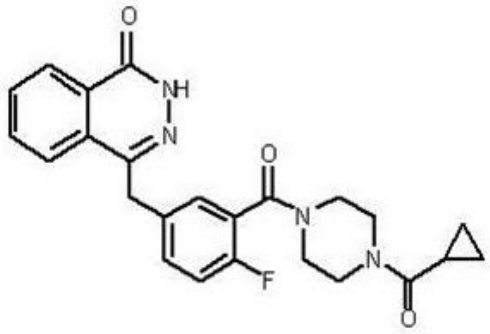
10 OVERDOSAGE

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

11 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 Lynparza 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.

Lynparza is available in 50 mg capsules for oral administration. Each capsule contains olaparib as the active ingredient and the following inactive ingredients:

- **Capsule content:** lauroyl polyoxylglycerides
- **Capsule shell:** hypromellose, titanium dioxide, gellan gum, potassium acetate
- **Capsule printing ink:** shellac, ferrosoferric oxide

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lynparza 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 complex, resulting in disruption of cellular homeostasis and cell death.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

Lynparza 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 C_{max} following a single 400 mg capsule dose were 37.2 µg*h/mL (N = 48) and 4.02 µg/mL (N = 48), respectively, and the steady state geometric mean AUC and C_{max} following 400 mg capsule twice daily were 43.5 µg*h/mL (N = 48) and 6.18 µg/mL (N = 48), respectively. Olaparib showed time-dependent PK that the steady state clearance decreased by 15% after multiple dosing.

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 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 11.9 ± 4.8 hours and apparent plasma clearance of 8.6 ± 7.1 L/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.

Drug Interactions

Based on the data from a drug-interaction trial (N=57), the AUC and C_{max} of olaparib increased by 2.7- and 1.4-fold, respectively, when olaparib was administered in combination with itraconazole, a strong CYP3A inhibitor. Simulations suggested that a moderate CYP3A inhibitor (fluconazole) may increase the AUC and C_{max} of olaparib by 2.2- and 1.2-fold, respectively.

Based on the data from a drug-interaction trial (N=22), the AUC and C_{max} of olaparib decreased by 87% and 71%, respectively, when olaparib was administered in combination with rifampicin, a strong CYP3A inducer. Simulations suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC and C_{max} of olaparib by approximately 50% and 30%, respectively.

In vitro studies have shown that olaparib is both an inhibitor and inducer of CYP3A and an inducer of CYP2B6. Olaparib is predicted to be a weak CYP3A substrate in humans. *In vitro* studies also indicated that olaparib is an inhibitor of UGT1A1, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown. *In vitro*, olaparib is a substrate of, and inhibits, the efflux transporter P-gp. 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 C_{max} 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 renal impairment trial, the mean AUC increased by 24% and the C_{max} increased 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).

13 NONCLINICAL TOXICOLOGY

13.1 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 Chinese hamster (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).

14 CLINICAL STUDIES

Advanced *gBRCA*-mutated Ovarian Cancer Treated with 3 or More Prior Lines of Chemotherapy

The efficacy of Lynparza was investigated in a single-arm study in patients with deleterious or suspected deleterious *gBRCAm* advanced cancers. A total of 137 patients with measurable, *gBRCAm* ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza capsules at a dose of 400 mg twice daily as monotherapy until disease progression or intolerable toxicity. Objective response rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST v1.0.

The median age of the patients was 58 years, the majority were White (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, *gBRCAm* status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the BRACAnalysis CDx™.

Efficacy results from Study 1 are summarized in Table 5.

Table 5 Overall Response and Duration of Response in Patients with *gBRCA*-mutated Advanced Ovarian Cancer Who Received 3 or More Lines of Chemotherapy

	N=137
Objective Response Rate (95% CI)	34% (26, 42)
Complete Response	2%
Partial Response	32%
Median DOR in months (95% CI)	7.9 (5.6, 9.6)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Lynparza 50 mg is a white, opaque, hard capsule, marked in black ink with: "OLAPARIB 50 mg" on the cap and AstraZeneca logo on the body; available in:

Bottles of 112 capsules NDC 0310-0657-58

16.2 Storage

Store at 25ºC (77°F), excursions permitted to 15ºC -30ºC (59°F -86°F) [*see USP Controlled Room Temperature*].

Lynparza should not be exposed to temperatures greater than 40ºC or 104ºF. Do not take Lynparza if it is suspected of having been exposed to temperatures greater than 40ºC or 104ºF.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Administration Instructions: Inform patients on how to take Lynparza *[see Dosage and Administration (2.3)]*. Lynparza should be taken twice daily with or without food. Instruct patients that if they miss a dose of Lynparza, not to take an extra dose to make up for the one that they missed. They should take their next normal dose at the usual time. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsule. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Lynparza *[see Drug Interactions (7.3)]*.
- Inform patients **not** to substitute Lynparza capsules (50 mg) with Lynparza tablets (100 mg and 150 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation *[see Dosage and Administration (2.1)]*.
- MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Lynparza *[see Warnings and Precautions (5.1)]*.

- Pneumonitis: Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing *[see Warnings and Precautions (5.2)]*.
- Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months after receiving the last dose *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.
- Lactation: Advise patients not to breastfeed while taking Lynparza and for one month after receiving the last dose *[see Use in Special Populations (8.2)]*.
- Nausea/Vomiting: Advise patients that mild or moderate nausea and/or vomiting is very common in patients receiving Lynparza and that they should contact their healthcare provider who will advise on available antiemetic treatment options.

Medication Guide
Lynparza (Lin-par-zah)
(olaparib)
capsules

What is the most important information I should know about Lynparza?

Lynparza may cause serious side effects, including:

Bone marrow problems called Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). Some people who have ovarian cancer or who have received previous treatment with chemotherapy, radiotherapy or certain other medicines for their cancer have developed MDS or AML during treatment with Lynparza. MDS or AML may lead to death. If you develop MDS or AML, your healthcare provider will stop treatment with Lynparza.

Symptoms of low blood cell counts are common during treatment with Lynparza, but can be a sign of serious bone marrow problems, including MDS or AML. Symptoms may include:

- weakness
- weight loss
- fever
- frequent infections
- blood in urine or stool
- shortness of breath
- feeling very tired
- bruising or bleeding more easily

Your healthcare provider will do blood tests to check your blood cell counts:

- before treatment with Lynparza
- every month during treatment with Lynparza
- weekly if you have low blood cell counts that last a long time. Your healthcare provider may stop treatment with Lynparza until your blood cell counts improve.

Lung problems (pneumonitis). Tell your healthcare provider if you have any new or worsening symptoms of lung problems, including shortness of breath, fever, cough, or wheezing. Your healthcare provider may do a chest x-ray if you have any of these symptoms. Your healthcare provider may temporarily stop treatment or completely stop treatment if you develop pneumonitis. Pneumonitis may lead to death.

What is Lynparza?

Lynparza is a prescription medicine used alone to treat women who have a certain type of abnormal inherited *BRCA* gene, advanced ovarian cancer, **and**:

- have received treatment with 3 or more prior types of chemotherapy.

Your healthcare provider will perform a test to make sure that Lynparza is right for you.

It is not known if Lynparza is safe and effective in children.

What should I tell my healthcare provider before taking Lynparza?

Before you take Lynparza, tell your healthcare provider about all of your medical conditions including if you:

- have lung or breathing problems
- have liver problems
- have kidney problems
- are pregnant or plan to become pregnant. Lynparza can harm your unborn baby and may cause loss of pregnancy (miscarriage).
  - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with Lynparza.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for 6 months after receiving the last dose of Lynparza.
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Lynparza passes into your breast milk. Do not breastfeed during treatment with Lynparza and for 1 month after receiving the last dose of Lynparza. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Lynparza and certain other medicines may affect how Lynparza works and may cause side effects.

How should I take Lynparza?

- Take Lynparza exactly as your healthcare provider tells you.
- Your healthcare provider may temporarily stop treatment with Lynparza or change your dose of Lynparza if you have side effects.
- Lynparza comes as capsules and tablets. **Lynparza capsules and tablets are not the same.** If your healthcare provider prescribes Lynparza capsules for you, **do not** take Lynparza tablets. If you have any questions about Lynparza, talk with your healthcare provider or pharmacist.
- Take Lynparza by mouth 2 times a day.
- Each dose should be taken 12 hours apart.
- Swallow Lynparza capsules whole. Do not chew, dissolve, or open the capsules.
- Take Lynparza with or without food.
- Do not take Lynparza capsules if they look damaged or show signs of leakage.
- If you miss a dose of Lynparza, take your next dose at your usual scheduled time. Do not take an extra dose to make up for a missed dose.
- If you take too much Lynparza, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking Lynparza?

- Avoid grapefruit, grapefruit juice, Seville oranges and Seville orange juice during treatment with Lynparza, since they may increase the level of Lynparza in your blood.

What are the possible side effects of Lynparza?

Lynparza may cause serious side effects.

See "**What is the most important information I should know about Lynparza?**"

The most common side effects of Lynparza are:

- nausea or vomiting. Tell your healthcare provider if you get nausea or vomiting. Your healthcare provider may prescribe medicines to treat these symptoms.
- low number of red or white blood cells
- tiredness or weakness
- pain or discomfort in the stomach area
- diarrhea
- changes in the way food tastes
- indigestion or heartburn
- headache
- loss of appetite
- changes in kidney function blood test
- sore throat or runny nose
- upper respiratory infection
- cough
- joint, muscle, and back pain
- rash
- decrease in platelets

These are not all the possible side effects of Lynparza. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Lynparza?

- Store Lynparza at room temperature, between 68°F to 77°F (20°C to 25°C).
- Do not store Lynparza at temperatures greater than 104°F (40°C). Do not take Lynparza if you think it may have been stored at a temperature greater than 104°F (40°C).

Keep Lynparza and all medicines out of the reach of children.

General information about the safe and effective use of Lynparza

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Lynparza for a condition for which it was not prescribed. Do not give Lynparza to other people, even if they have the same symptoms you have. It may **harm** them.
You can ask your healthcare provider or pharmacist for information about Lynparza that is written for health professionals.

What are the ingredients in Lynparza?

Active ingredient: olaparib

Inactive ingredients:
Capsule contains: lauroyl polyoxylglycerides
Capsule shell contains: hypromellose, titanium dioxide, gellan gum, potassium acetate
Capsule printing ink contains: shellac, ferrosoferric oxide

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
For more information, call 1-800-236-9933 or go to www.Lynparza.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 10/2017