CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206162Orig1s000

<u>LABELING</u>

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

---------- INDICATIONS AND USAGE ----------
Lynparza is a poly (ADP-ribose) polymerase (PARP) inhibitor 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. (1.1)

The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1, 14)

---------- DOSAGE AND ADMINISTRATION ----------
- Recommended dose is 400 mg taken twice daily. (2.2)
- Continue treatment until disease progression or unacceptable toxicity. (2.2)
- For adverse reactions, consider dose interruption of treatment or dose reduction. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------
Capsules: 50 mg (3)

---------- CONTRAINDICATIONS ----------
None

---------- WARNINGS AND PRECAUTIONS ----------
- Myelodysplastic syndrome/Acute Myeloid Leukemia: (MDS/AML) occurred in patients exposed to Lynparza, and some cases were fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/AML is confirmed. (5.1)
- Pneumonitis: occurred in 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 avoid pregnancy. (5.3, 8.1)

---------- ADVERSE REACTIONS ----------
- Most common adverse reactions (≥20%) in clinical trials were anemia, nausea, fatigue (including asthenia), vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis/pharyngitis/URI, cough, arthralgia/musculoskeletal pain, myalgia, back pain, dermatitis/rash and abdominal pain/discomfort. (6.1)
- Most common laboratory abnormalities (≥25%) were increase in creatinine, mean corpuscular volume elevation, decrease in hemoglobin, decrease in lymphocytes, decrease in absolute neutrophil count, 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 and moderate CYP3A inhibitors. If the inhibitor cannot be avoided, reduce the dose. (2.3, 7.2)
- 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. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------
- Nursing Mothers: Discontinue treatment or discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: 12/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of g*BRCA*-mutated advanced ovarian cancer

Lynparza 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.

The indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 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.

2.2 Recommended Dosing

The recommended dose of Lynparza 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 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)]*.

2.3 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.

2.4 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)]*.

3 DOSAGE FORMS AND STRENGTHS

Lynparza (olaparib) is supplied as a white, opaque, hard capsule (50 mg), 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

Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) have been confirmed in 6 out of 298 (2%) patients enrolled in a single arm trial of Lynparza monotherapy, in patients with deleterious or suspected deleterious germline *BRCA*-mutated (*gBRCA*m) advanced cancers. In a randomized placebo controlled trial, MDS/AML occurred in 3 out of 136 (2%) patients with advanced ovarian cancer treated with Lynparza. Overall, MDS/AML were reported in 22 of 2,618 (<1%) patients treated with Lynparza. The majority of MDS/AML cases (17 of 22 cases) were fatal, and the duration of therapy with Lynparza in patients who developed secondary MDS/cancer-therapy related AML varied from <6 months to >2 years. All patients had previous chemotherapy with platinum agents and/or other DNA damaging agents.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤CTCAE Grade 1). For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to CTCAE Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue 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, fever, cough, wheezing, or a radiological abnormality occurs, interrupt treatment with Lynparza and initiate prompt investigation. If pneumonitis is confirmed, discontinue Lynparza.

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. 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 the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to avoid becoming pregnant while taking Lynparza. If contraceptive methods are being considered, use effective contraception during treatment and for at least one month after receiving the last dose of Lynparza *[see Use in Specific Populations (8.6)]*.

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.

Lynparza 400 mg twice daily as monotherapy, has been studied in 300 patients with g*BRCA*-mutated advanced ovarian cancer, and 223 of these patients had received 3 or more prior lines of chemotherapy.

In the 223 patients with g*BRCA*-mutated ovarian cancer who received 3 or more prior lines of chemotherapy (including 137 patients in Study 1 with measureable disease) *[see Clinical Studies (14)]* adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. 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. Table 1 presents the frequency of adverse reactions reported in ≥20% of 223 patients (in 6 studies) with g*BRCA*-mutated advanced ovarian cancer who had received 3 or more prior lines of chemotherapy who were treated with Lynparza 400 mg twice daily. The median exposure to Lynparza in these patients was 158 days.

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

	3 or more lines of prior chemotherapy	
Adverse Reaction	Grades 1-4 N=223 %	Grades 3-4 N=223 %
Blood and Lymphatic disorders		
Anemia	34	18
Gastrointestinal disorders		
Abdominal pain/discomfort	43	8
Decrease 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 presents the frequency of abnormal laboratory findings in the 223 patients with g*BRCA*-mutated advanced ovarian cancer who had received three or more prior lines of chemotherapy receiving Lynparza 400 mg twice daily.

Table 2 Laboratory Abnormalities Reported in Patients with gBRCA-Mutated Advanced Ovarian Cancer Receiving Lynparza

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

* Patients were allowed to enter clinical studies with laboratory values of CTCAE 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, dysguesia, 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, hyperglycemia, anxiety, depression, insomnia, dysuria, urinary

incontinence, vulvovaginal disorder, dry skin/ eczema, pruritis, hypertension, venous thrombosis (including pulmonary embolism), and hot flush.

Table 3 presents adverse reactions reported in ≥20% of patients from a randomized trial of Lynparza 400 mg twice daily as maintenance monotherapy compared to placebo in patients with platinum sensitive, relapsed, high-grade serous ovarian cancer following treatment with 2 or more platinum-containing regimens. Table 4 presents the laboratory abnormalities in patients from this randomized trial. Of the 96 patients with g*BRCA*-mutation, 53 received Lynparza, and 43 received placebo. The median duration on treatment with Lynparza was 11.1 months for patients with a g*BRCA* mutation compared to 4.4 months for patients with g*BRCA* mutation on placebo.

Adverse reactions led to dose interruptions in 26% of those receiving Lynparza and 7% of those receiving placebo; dose reductions in 15% of Lynparza and 5% of placebo patients; and discontinuation in 9% of Lynparza and 0% in placebo patients. One (2%) patient on Lynparza died as a result of an adverse reaction.

Table 3 Adverse Reactions Reported in ≥20% of Patients with gBRCA-Mutated Ovarian Cancer in the Randomized Trial

Adverse Reactions	Lynparza N=53		Placebo N=43	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and Lymphatic disorders				
Anemia	25	4	7	2
Gastrointestinal disorders				
Abdominal pain/discomfort	47	0	58	2
Decreased appetite	25	0	14	0
Nausea	75	2	37	0
Vomiting	32	4	9	0
Diarrhea	28	4	21	2
Dyspepsia	25	0	14	0
Dysgeusia	21	0	9	0
General disorders				
Fatigue (including asthenia, lethargy)	68	6	53	2
Infections and infestations				
Nasopharyngitis/Pharyngitis/URI	43	0	16	0
Musculoskeletal and Connective tissue disorders				
Arthralgia/Musculoskeletal pain	32	4	21	0
Myalgia	25	2	12	0
Back pain	25	6	21	0
Nervous system disorder				
Headache	25	0	19	2
Respiratory, Thoracic, Mediastinal disorders				
Cough	21	0	14	0
Skin and Subcutaneous Tissue				
Dermatitis/Rash	25	0	14	0

Table 4 Laboratory Abnormalities in Patients with gBRCA-Mutated Ovarian Cancer in the Randomized Trial

Laboratory parameter*	Lynparza	Placebo

	N=53		N=43	
	Grades 1-4 %	**Grades 3-4 %**	**Grades 1-4 %**	**Grades 3-4 %**
Decrease in hemoglobin	85	8	58	2
Decrease in absolute neutrophil count	32	8	23	0
Decrease in platelets	26	6	19	0
Mean corpuscular volume elevation	85	-	44	-
Increase in creatinine*	26	0	5	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

7 DRUG INTERACTIONS

Olaparib is primarily metabolized by CYP3A.

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

In patients (N=57), co-administration of itraconazole, a strong CYP3A inhibitor, increased AUC of olaparib by 2.7-fold. A moderate CYP3A inhibitor, fluconazole, is predicted to increase the AUC of olaparib by 2-fold.

Avoid concomitant use of strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir/ritinovir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil). If the strong or moderate CYP3A inhibitors must be co-administered, reduce the dose of Lynparza *[see Dosage and Administration (2.4)]*.

Avoid grapefruit and Seville oranges during Lynparza treatment *[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 50-60%.

Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin). If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy of Lynparza *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.3)]*

Risk summary

Lynparza 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.

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 11% of the human exposure (AUC_{0-24h}) 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_{0-24h}) 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.

8.3 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

In clinical studies of Lynparza enrolling 735 patients with advanced solid tumors [the majority (69%) of whom had ovarian cancer] who received Lynparza 400 mg twice daily as monotherapy, 148 (20%) of patients were aged ≥65 years. The safety profile was similar irrespective of age with the exception of AEs of CTCAE ≥3 which were reported more frequently in patients aged ≥65 years (53.4%) than those <65 years (43.4%). No individual adverse event or System Organ Class accounted for this observed difference.

8.6 Females of Reproductive Potential

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to avoid pregnancy while taking Lynparza. If contraceptive methods are being considered, use highly effective contraception during treatment with Lynparza and for at least one month following the last dose of Lynparza. Instruct patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking Lynparza.

8.7 Hepatic Impairment

The effect of hepatic impairment on exposure to Lynparza has not been studied. Patients with bilirubin >1.5 X ULN and AST/ALT ≥2.5 X ULN (≥5 X ULN in the presence of liver metastases) were excluded from Lynparza clinical trials. There are no data in patients with baseline hepatic impairment (serum bilirubin >1.5 X ULN) *[see Clinical Pharmacology (12.3)]*.

8.8 Renal Impairment

Based on preliminary data, a 1.5 fold increase in mean exposure (AUC) was observed in patients with mild renal impairment (CLcr = 50-80 mL/min) compared to patients with normal renal function (CLcr >80 mL/min). No dose adjustment to the starting dose is required in patients with CLcr 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 (CLcr <50 mL/min) or patients on dialysis *[see Clinical Pharmacology (12.3)]*.

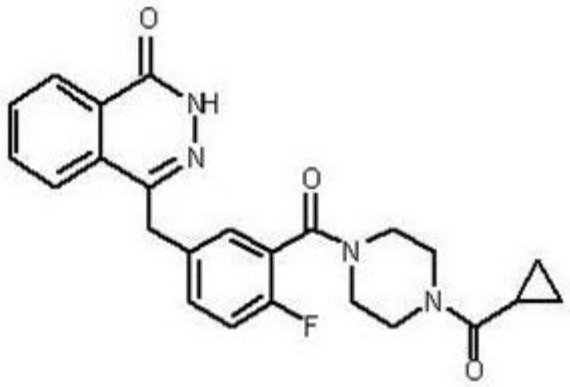
10 OVERDOSAGE

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 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.

12.3 Pharmacokinetics

Absorption

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

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 (CLcr = 50-80 mL/min; N=14) compared to those with normal renal function (CLcr >80 mL/min; N=8). There are no data in patients with CLcr < 50 mL/min or in patients on dialysis.

Drug Interactions

In vitro, olaparib was an inhibitor of CYP3A4 and an inducer of CYP2B6 at higher concentrations than are clinically achieved. Olaparib produced little/no inhibition of other CYP isozymes. *In vitro* studies have shown that olaparib is a substrate of CYP3A4.

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 using physiologically-based pharmacokinetic (PBPK) models suggested that a moderate CYP3A inhibitor (fluconazole) may increase the AUC and C_{max} of olaparib by 2- and 1.1-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 using PBPK models suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC and C_{max} of olaparib by 50 - 60% and 20 - 30%, respectively.

In vitro studies have shown that olaparib is a substrate of P-gp and an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown.

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 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

The efficacy of Lynparza was investigated in a single-arm study in patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced cancers (Study 1). A total of 137 patients with measurable, g*BRCA*m-associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received Lynparza 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 v1.1.

The median age of the patients was 58 years, the majority were Caucasian (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, germline *BRCA* mutation status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDx™, which is FDA approved for selection of patients for Lynparza treatment.

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 Prior Lines of Chemotherapy in Study 1

	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 15-30ºC (59-86ºF) [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

SEE FDA-APPROVED PATIENT LABELING (MEDICATION GUIDE)

- Dosing Instructions: Inform patients on how to take Lynparza *[see Dosage and Administration (2.1)]*. Lynparza should be taken twice daily. 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. Patient should not take Lynparza with grapefruit or Seville oranges.

- 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)]*.

- Pregnancy and Females of Reproductive Potential: 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 at least one month after receiving the last dose of Lynparza *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.6)]*.

- Nursing Mothers: Advise patients not to breastfeed while taking Lynparza *[see Use in Special Populations (8.3)]*.

- 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

Read this Medication Guide before you start taking Lynparza and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

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

Lynparza may cause serious side effects that can lead to death, 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 or certain other medicines for their cancer have developed MDS or AML during treatment with Lynparza. 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.

Tell your healthcare provider if you have any of the symptoms above during treatment with Lynparza.

What is Lynparza?

Lynparza is a prescription medicine used to treat women with advanced ovarian cancer who:

- have received previous treatment with 3 or more prior chemotherapy medicines or a combination of chemotherapy medicines for their cancer, **and**
- have a certain type of abnormal inherited BRCA gene.

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 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)**. You should not become pregnant during treatment with Lynparza. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with Lynparza and for at least 1 month 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 or think you may be pregnant during treatment with Lynparza.
- are breastfeeding or plan to breastfeed. It is not known if Lynparza passes into your breast milk. You and your healthcare provider should decide if you will take Lynparza or breastfeed. You should not do both.

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.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

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.
- Take Lynparza 2 times a day.
- Swallow Lynparza capsules whole. Do not chew, dissolve, or open the capsules.
- 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 emergency room right away.

What should I avoid while taking Lynparza?

- Avoid grapefruit, grapefruit juice and Seville oranges during treatment with Lynparza. Grapefruit and Seville oranges 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.
- tiredness or weakness
- diarrhea
- indigestion or heartburn
- headache
- loss of appetite
- changes in the way food tastes
- changes in kidney function blood test
- sore throat or runny nose
- upper respiratory infection
- cough
- pain in the joints, muscles, and back
- rash
- pain or discomfort in the stomach area

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Lynparza. For more information, ask your healthcare provider or pharmacist.

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 to 77°F (20 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.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Lynparza that is written for health professionals.

For more information, call 1-800-236-9933 or go to www.Lynparza.com.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By: Patheon Pharmaceuticals, Inc.
Cincinnati, OH 45237
Issued: 12/2014

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AREA RESERVED FOR LOT/EXP

NDC 0310-0657-58

Lynparza™
(olaparib) capsules

Rx only

Swallow capsule whole. Do not chew, dissolve or open capsule.

50 mg

448 capsules
(4 bottles of 112 capsules)

Oral use

AstraZeneca

NDC 0310-0657-58

Lynparza™
(olaparib) capsules

50 mg

448 capsules
(4 bottles of 112 capsules)

Oral use

Rx only

AstraZeneca

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Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
By: Patheon Pharmaceuticals, Inc.
Cincinnati, OH 45237
Product of Switzerland

AstraZeneca

AstraZeneca

XXXXX-XX

Position Pharmacy Label over this panel

Each capsule contains 50 mg of olaparib.
Swallow capsule whole. Do not chew, dissolve or open capsule.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP].
Do not expose to temperatures greater than 40°C or 104°F.

NDC 0310-0657-58

Lynparza™
(olaparib) capsules

Rx only

50 mg

448 capsules
(4 bottles of 112 capsules)

Oral use

AstraZeneca

AstraZeneca

Colors used need to be redacted; I also redacted the software used by the sponsor.

Lynparza 50mg 112ct x 4ct carton

Material No. XXXXX-XX
Dimensions:
CR/LRF No. 43258 / 2014.02924
Colors (b) (4)
Plate Date 10/30/14 5:52 pm PK
AstraZeneca

PRINTER NOTES:

- Software Used: (b) (4)
- Fonts used have been outlined.
- Barcode specifications: I 2 of 5 (reading 2 03 0310 0657 58 2); I 2 of 5 (reading 03730500) narrow bar = 15.5, ratio = 2.5, bwa= -2 mils, magnification= 39%
  The use of barcodes provided in artwork is optional. Replace if barcode specifications do not meet press requirements.
- Component Information Box and Printer Notes are for placement only, do not print.
- Cyan dieline in dieline layer is for placement only, do not print.

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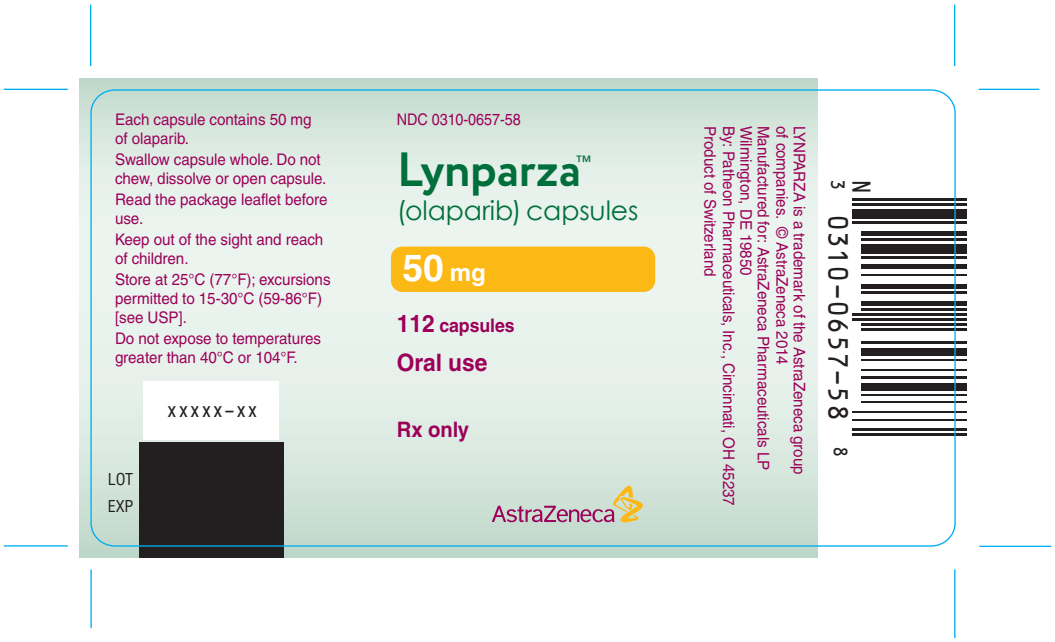

Lynparza 50mg 112ct bottle label

Material No. XXXXX-XX	**Colors** (b) (4)
Dimensions: 2-3/8" x 4-1/2"	
CR/LRF No. 43258 / 2014.02924	
Plate Date 10/30/14 5:52 pm PK	AstraZeneca

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PRINTER NOTES:

- Software Used: (b) (4)
- Fonts used have been outlined.
- Barcode specifications: 12-digit UPC (reading 3 0310 0657 58 8), bwa= -2 mils, magnification= 100%

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