PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr LYNPARZA®

olaparib capsules

50 mg

Antineoplastic agent

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Pr LYNPARZA®

olaparib capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
oral	capsule 50 mg	Gellan gum (E418), Hypromellose, Iron oxide black (E172), Lauroyl macrogol-32 glycerides, Potassium acetate, Shellac, Titanium dioxide (E171)

INDICATIONS AND CLINICAL USE

LYNPARZA (olaparib capsules) is indicated as:

- monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) *BRCA*-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

  Platinum-sensitive relapse is defined as disease progression occurring at least 6 months following completion of platinum chemotherapy.

Marketing authorization was based on results from a randomized double-blind, placebo controlled Phase II trial (Study 19) demonstrating that LYNPARZA is superior to placebo in prolonging PFS in patients with *BRCA*-mutated PSR ovarian cancer, as assessed by investigator using RECIST 1.0 (see CLINICAL TRIALS).

Patients must have confirmation of a breast cancer susceptibility gene mutation (*BRCA* mutation) (germline or somatic) before LYNPARZA (olaparib capsules) treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test methodology.

LYNPARZA Capsules Controlled Distribution Program
LYNPARZA capsules are only supplied through a controlled distribution program, and patients should be enrolled in the AstraZeneca Oncology Patient Support Program to continue to receive LYNPARZA capsules. For more information, please call toll free 1-877-280-6208. Physicians and dispensers should encourage their patients to register in the AstraZeneca

Oncology Patient Support Program as additional counselling and follow-up will be offered to reduce the risk of medication errors due to the dual availability of the tablet formulation as there are differences in dosing and bioavailability of each formulation (see DOSAGE AND ADMINISTRATION, Risk of Medication Error).

Geriatrics (>65 years of age):
There is limited clinical data in patients aged 65 years and over.

Pediatrics (< 18 years of age):

The safety and efficacy of LYNPARZA in children and adolescents have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the capsule. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Treatment with LYNPARZA (olaparib) should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.
- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) has been reported in patients exposed to LYNPARZA. The majority of the reports have been fatal. (See WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).
- Pneumonitis has been reported in a small number of patients receiving LYNPARZA, and some reports have been fatal. (See WARNINGS AND PRECAUTIONS, Respiratory).
- There is a risk of medication errors between LYNPARZA capsules and tablets. To avoid medication error, prescribers should specify the formulation and dosage of LYNPARZA on each prescription. Do not substitute LYNPARZA capsules with LYNPARZA tablets on a milligram-to-milligram basis due to differences in dosing and bioavailability of each formulation (see DOSAGE AND ADMINISTRATION, Dosing Considerations for Capsule).
- LYNPARZA could cause fetal harm when administered to a pregnant woman. (See WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

General

Interactions with other medicinal products

Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced.

Co-administration of LYNPARZA with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving LYNPARZA requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of LYNPARZA may be substantially reduced.

See DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION.

Carcinogenesis and Mutagenesis

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was reported with an incidence of <1.5% in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow-up, and the majority of events had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging treatments. The majority of reports were in germline *BRCA* mutation carriers and some of the patients had a history of more than one primary malignancy or of bone marrow dysplasia. If MDS and/or AML or other clonal blood disorders are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately.

Hematologic

Hematological toxicity has been reported in patients treated with LYNPARZA, including clinical diagnoses and/or laboratory findings of generally mild or moderate (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2) anemia, neutropenia, thrombocytopenia and lymphopenia. Grade 3 or higher toxicity has been reported, including hemorrhagic stroke associated with thrombocytopenia. Patients should not start treatment with LYNPARZA until they have recovered from hematological toxicity caused by previous anti-cancer therapy (hemoglobin, platelet, and neutrophil levels should be ≤ CTCAE grade 1). Baseline testing, followed by monthly monitoring of complete blood counts, is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

If a patient develops severe hematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate hematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of LYNPARZA dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Respiratory

Pneumonitis (grade 3 or higher) has been reported in < 1.0% of patients treated with LYNPARZA monotherapy in clinical studies. The reports of pneumonitis had no consistent

clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When LYNPARZA was used in clinical studies in combination with other therapies, there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological chest abnormality occurs, LYNPARZA treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

Reproduction

Embryofetal toxicity

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause fetal harm when administered to a pregnant woman. Studies in rats have shown that olaparib caused embryofetal toxicity that included increases in post implantation loss and teratogenic effects at exposures below those of patients receiving LYNPARZA at the recommended human dose of 400 mg twice daily (see WARNINGS AND PRECAUTIONS, Special Populations and TOXICOLOGY).

Special Populations

Patients with Hepatic Impairment

Based on results of a pharmacokinetic study which showed no clinically significant change in exposure in patients with mild or moderate hepatic impairment, LYNPARZA (olaparib capsules) can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment. LYNPARZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Patients with Renal Impairment

Based on pharmacokinetic modeling, the recommended reduced total daily dose of LYNPARZA (olaparib capsules) for patients with moderate renal impairment (creatinine clearance 31-50 mL/min) is 600 mg taken as six 50 mg capsules twice daily (see DOSAGE AND ADMINISTRATION). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 mL/min), as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51-80 mL/min) with no dose adjustment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Pregnant Women

There are no clinical data regarding the use of LYNPARZA in pregnant women. LYNPARZA should not be used during pregnancy due to the potential teratogenic, genotoxic, and lethal embryofetal effects (see TOXICOLOGY).

If a patient becomes pregnant while receiving LYNPARZA, the patient should be apprised of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

Contraception and pregnancy testing

Women of childbearing potential must use effective contraception during therapy and for one month after receiving the last dose of LYNPARZA due to the teratogenic and genotoxic potential of LYNPARZA. A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at one month after receiving the last dose of LYNPARZA.

Nursing Women

There are no data on the use of LYNPARZA in breast-feeding women. The excretion of LYNPARZA in milk has not been studied in animals or in breast-feeding mothers. Breast-feeding mothers are advised not to breast-feed during treatment with LYNPARZA and for one month after the last dose of LYNPARZA.

Monitoring and Laboratory Tests

BRCA Testing

Patients must have confirmation of a deleterious or suspected deleterious breast cancer susceptibility gene mutation (germline or somatic *BRCA* mutation) before LYNPARZA treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method.

Hematologic Testing

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment (see WARNINGS AND PRECAUTIONS, Hematologic).

If a patient develops severe hematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate hematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of LYNPARZA dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Pregnancy Testing

A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at one month after receiving the last dose of LYNPARZA.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Tabulated List of ADRs from Pooled Clinical Trials

The safety of LYNPARZA (olaparib) was evaluated in a pooled safety dataset of 2095

patients with solid tumours treated with LYNPARZA monotherapy (capsule and tablet formulation) in clinical trials at the recommended dose. The overall safety profile of the two formulations are similar.

The most commonly reported adverse reactions (in ≥20% of patients) from LYNPARZA monotherapy pooled studies (n=2095) were nausea, fatigue (including asthenia), vomiting, anemia, diarrhea and decreased appetite. These reactions were generally CTCAE grade 1 or 2, intermittent in nature and managed by standard supportive treatments or LYNPARZA dose modification. The most commonly reported adverse reactions (in ≥1% of patients) with CTCAE grade ≥3 severity were anemia, fatigue (including asthenia), neutropenia, abdominal pain, leukopenia, vomiting, neutrophil count decreased, thrombocytopenia, nausea, diarrhea, dyspnea, white blood cell count decreased, and hemoglobin decreased.

The most commonly reported serious adverse events (in ≥1% of patients) were: anemia (4.2%), abdominal pain (1.1%), vomiting (1.1%) and small intestinal obstruction (1.0%).

Nausea was generally reported very early, with first onset within the first month of LYNPARZA treatment in the majority of affected patients. Vomiting was reported early, with first onset within the first two months of LYNPARZA treatment in the majority of affected patients. Most of these events improved over time while continuing LYNPARZA without the need for medical intervention.

The overall frequency of adverse events leading to discontinuation of LYNPARZA was 7.0%. The frequencies of adverse reactions (in >0.2% of patients) leading to discontinuation of LYNPARZA treatment were anemia (1.2%), nausea (0.7%), vomiting (0.6%), fatigue (including asthenia) (0.5%), thrombocytopenia (0.4%) and neutropenia (0.3%).

Hematological toxicity

Anemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between LYNPARZA (olaparib) and decreases in hemoglobin has been demonstrated. Other hematological toxicities were generally CTCAE grade 1 or 2, however, there were reports of CTCAE grade 3 and higher events.

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the upper limit of normal was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Other laboratory findings

Data from a double-blind placebo-controlled study showed median increase in blood creatinine up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. Ninety percent of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study 19

Study 19 is a Phase II randomised, double-blind placebo-controlled study of olaparib capsule dose of 400 mg twice daily maintenance monotherapy in patients with platinum-sensitive relapsed (PSR) serous ovarian cancer (Study 19, n=264 [n=136 on olaparib and n=128 on placebo]). The median total treatment duration in all patients was 8.7 months in the olaparib group and 4.6 months for placebo.

Table 1 shows the adverse drug reactions associated with LYNPARZA capsules from the pivotal Study 19 with frequencies reported regardless of causality.

Table 1 Adverse Drug Reactions Reported in Study 19 (Safety Analysis Set)

Preferred term	LYNPARZA 400 mg capsules twice daily N=136		Placebo N=128	
	All Grades	Grade 3 and higher	All Grades	Grade 3 and higher
Blood & Lymphatic Disorders				
Anemia[a]	31 (22.8)	10 (7.4)	9 (7.0)	1 (0.8)
Neutropenia[a]	7 (5.1)	5 (3.7)	7 (5.5)	2 (1.6)
Thrombocytopenia[a]	5 (3.7)	1 (0.7)	3 (2.3)	0
Leukopenia[a]	3 (2.2)	3 (2.2)	2 (1.6)	0
Lymphopenia[a]	1 (0.7)	0	0	0
Gastrointestinal Disorders				
Nausea	96 (70.6)	3 (2.2)	46 (35.9)	0
Vomiting	48 (35.3)	3 (2.2)	18 (14.1)	1 (0.8)
Diarrhea	37 (27.2)	3 (2.2)	31 (24.2)	3 (2.3)
Dyspepsia	27 (19.9)	0	11 (8.6)	0
Upper abdominal pain	25 (18.4)	0	11 (8.6)	1 (0.8)
Stomatitis	12 (8.8)	0	4 (3.1)	0

Table 1 Adverse Drug Reactions Reported in Study 19 (Safety Analysis Set)

Preferred term	LYNPARZA 400 mg capsules twice daily N=136		Placebo N=128	
	All Grades	Grade 3 and higher	All Grades	Grade 3 and higher
General Disorders				
Fatigue (including asthenia)	86 (63.2)	12 (8.8)	59 (46.1)	4 (3.1)
Investigations				
Increase in blood creatinine	9 (6.6)	0	2 (1.6)	0
Mean corpuscular volume elevation	0	0	0	0
Metabolism & Nutrition Disorders				
Decreased appetite	29 (21.3)	0	17 (13.3)	0
Nervous System Disorders				
Headache	29 (21.3)	0	17 (13.3)	1 (0.8)
Dysgeusia	22 (16.2)	0	8 (6.3)	0
Dizziness	21 (15.4)	0	9 (7.0)	0
Respiratory, Thoracic & Mediastinal Disorders				
Cough[a]	27 (19.9)	0	13 (10.2)	0

a represents a grouped term
The table includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.
The severity of the adverse events was graded based on the CTCAE version 3.
MedDRA Version 19.

The most commonly reported adverse events that led to dose modification were: nausea (10.3%), vomiting (10.3%), fatigue (8.8%), anemia (6.6%), diarrhea (4.4%), abdominal pain (3.7%), dyspnea (2.9%), asthenia (2.9%), neutropenia (2.9%), leukopenia (2.2%) and thrombocytopenia (2.2%).

Serious Adverse Events

In Study 19, the most commonly reported serious adverse events (≥1%) in patients treated with olaparib 400 mg twice daily as maintenance therapy were anemia (2.2%), pancytopenia (1.5%), constipation (1.5%), small intestinal obstruction (1.5%), femur fracture (1.5%) and dyspnea (1.5%).

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment.

Table 2 Laboratory Abnormalities Reported in ≥25% of Patients in Study 19

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

a Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
b Represents the proportion of subjects whose mean corpuscular volume was > upper limit of normal (ULN).
CTCAE Common Terminology Criteria for Adverse Events

Mean corpuscular volume (MCV)

In Study 19, 82.4% olaparib treated patients compared to 50.8% placebo treated patients had an on treatment MCV above the upper limit of normal (ULN), irrespective of baseline MCV value. At baseline 47.8% patients on the olaparib arm and 52.4% patients on the placebo arm had MCV values below the ULN and in these patients, 64.6% olaparib and 13.6% placebo patients had MCV elevation to >ULN on treatment. Levels appeared to return to <ULN upon treatment discontinuation and did not appear to have any clinical consequences.

Increase in blood creatinine

Median blood creatinine levels in the LYNPARZA group from Study 19 increased up to 23% from baseline, remained consistent over time and returned to baseline after treatment discontinuation, with no apparent clinical sequelae. At baseline, 90% of patients had

creatinine values of CTCAE grade 0 and 10% had CTCAE grade 1 values. The majority of patients in this study had baseline and on-treatment urea and BUN levels within normal range.

Tabulated list of adverse drug reactions from pooled clinical trials

The safety profile is based on pooled data from 2095 patients with solid tumours treated with LYNPARZA monotherapy in clinical trials at the recommended dose.

The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organized by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 3. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

Table 3 Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Blood and lymphatic system disorders	Anemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Very common	Common
	Lymphopenia[a]	Common	Uncommon
Immune system disorders	Rash[a]	Common	-
	Hypersensitivity[a]	Uncommon	-
	Dermatitis[a]	Uncommon	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Very common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Uncommon
	Mean cell volume increased	Uncommon	-

a represents a grouped term

DRUG INTERACTIONS

Overview

Clinical studies of LYNPARZA (olaparib) in combination with other anti-cancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anti-cancer agents.

Olaparib is predominantly metabolised by CYP3A (see ACTION AND CLINICAL PHARMACOLOGY). Co-administered CYP3A inhibitors or inducers may respectively increase or decrease olaparib plasma concentration.

In vitro, olaparib is an inhibitor and inducer of CYP3A4 and an inducer of CYP2B6. Olaparib is a weak CYP3A inhibitor *in vivo*. It also inhibits drug transporter proteins OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K (see ACTION AND CLINICAL PHARMACOLOGY).

Drug-Drug Interactions

The drugs listed in this table are based on either PBPK modeling reports, drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Drugs that may affect the exposure to olaparib)			
Strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin, telithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir)	CT/T	In patients, a co-administered strong CYP3A inhibitor increased olaparib mean C_{max} and mean AUC.	Co-administration is not recommended. If it must be co-administered, the dose of LYNPARZA should be reduced (see DOSAGE AND ADMINISTRATION).
Strong inducers of CYP3A (e.g., rifampicin, phenobarbital, phenytoin, rifabutin, rifapentine, carbamazepine, nevirapine)	CT/T	In patients, a co-administered strong CYP3A inducer decreased olaparib mean C_{max} and mean AUC.	Co-administration is not recommended. If a strong CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of LYNPARZA (see WARNINGS AND PRECAUTIONS).
Moderate inhibitors of CYP3A (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil)	T	Olaparib is predominantly metabolised by CYP3A. Moderate CYP3A inhibitors may increase the exposure to olaparib when co-administered.	Co-administration is not recommended. If it must be co-administered, the dose of LYNPARZA should be reduced (see DOSAGE AND ADMINISTRATION).
Moderate inducers of CYP3A (e.g., bosentan, efavirenz, etravirine, modafinil)	T	Olaparib is predominantly metabolised by CYP3A. Moderate CYP3A inducers may decrease the exposure to olaparib when co-administered.	Co-administration is not recommended. If a moderate CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of LYNPARZA.

Table 4 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Drugs for which the exposure may be affected by olaparib)			
Substrates of CYP2B6 (e.g., bupropion and efavirenz)	T	Olaparib induces CYP2B6 *in vitro;* olaparib may decrease the exposure to co-administered substrates of CYP2B6.	Caution should be exercised when co-administered. Patients should be closely monitored.
Substrates of CYP3A (e.g., simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, quetiapine and midazolam)	T/CT	Olaparib is predicted to be a weak CYP3A inhibitor *in vivo*; olaparib may increase the exposure to substrates of CYP3A through enzyme inhibition when co-administered.	Caution should be exercised when co-administered as exposure to substrates may be increased. Patients should be closely monitored (see WARNINGS AND PRECAUTIONS).
Substrates of hepatic uptake transporters OATP1B1, OCT1 (e.g., bosentan, glibenclamide, repaglinide, statins, valsartan, metformin)	T	Olaparib inhibits OATP1B1 and OCT1 *in vitro*; olaparib may increase the exposure of substrates of these transporters when co-administered.	Caution should be exercised when co-administered - especially in combination with any statin. Patients should be closely monitored.
Substrates of renal uptake transporters OCT2, OAT3, MATE1 and MATE2K (e.g., furosemide, methotrexate, metformin, cisplatin, amantadine and cimetidine)	T	Olaparib inhibits OCT2, OAT3, MATE1, and MATE2K *in vitro*; olaparib may increase the exposure of substrates of these transporters when co-administered.	Caution should be exercised when co-administered. Patients should be closely monitored.

Table 4 Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Pharmacodynamic Interactions			
Myelosuppressive anticancer agents, including DNA damaging agents	CT	Potentiation and prolongation of myelo-suppressive toxicity.	LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anticancer agents.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical / PBPK modelling
Acronyms: MDR1 = Multi-Drug Resistance protein-1; OATP1B1 = Organic Anion Transporter polypeptide 1B1; OCT1 or OCT2 = Organic Cation Transporter-1 or -2; OAT 3 = Organic Anion Transporter 3, MATE1 or MATE2K = multidrug and toxin extrusion protein-1 or -2
See ACTION AND CLINICAL PHARMACOLOGY

Drug-Food Interactions

Co-administration of olaparib with a high fat meal slowed the rate of absorption (median T_{max} delayed by 2 hours) and increased the extent of absorption of olaparib (mean AUC increased by approximately 20%). Consequently, patients should take LYNPARZA at least one hour after food, and should refrain from eating for 2 hours afterwards (see DOSAGE AND ADMINISTRATION).

Patients should avoid grapefruit, star fruit, pomegranate and Seville oranges or their juices, which are known to inhibit CYP3A, during LYNPARZA treatment as these may increase olaparib plasma concentration.

Drug-Herb Interactions

Co-administration of St. John's Wort, a potent inducer of CYP3A, may decrease exposure to olaparib and should be avoided.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Life Style Interactions

Asthenia, fatigue and dizziness have been reported in patients receiving LYNPARZA treatment. Patients experiencing these symptoms should use caution when driving or operating machines.

DOSAGE AND ADMINISTRATION

Risk of Medication Error

There is a risk of medication errors between LYNPARZA capsules and LYNPARZA tablets. In order to minimize this risk, check the bottle labels to ensure that the drug being prepared and dispensed is LYNPARZA capsules and not LYNPARZA tablets. Prescribers should

specify the formulation and dosage of LYNPARZA on each prescription (see OVERDOSAGE).

LYNPARZA Capsules Controlled Distribution Program

LYNPARZA capsules are only supplied through a controlled distribution program, and patients should be enrolled in the AstraZeneca Oncology Patient Support Program to continue to receive LYNPARZA capsules. For more information, please call toll free 1-877-280-6208. Physicians and dispensers should encourage their patients to register in the AstraZeneca Oncology Patient Support Program as additional counselling and follow-up will be offered to reduce the risk of medication errors due to the dual availability of the tablet formulation as there are differences in dosing and bioavailability of each formulation.

Dosing Considerations for Capsule

- ***Non-Interchangeability between LYNPARZA Capsules and LYNPARZA Tablets***
  LYNPARZA (olaparib capsules) is also available as 100 mg and 150 mg olaparib tablet formulations. Refer to Table 5 and the LYNPARZA tablets Product Monograph for specific dosing information. 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 (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, the specific dosage recommendations for each formulation should be followed.

- Treatment with LYNPARZA should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

- Patients must have confirmation of a breast cancer susceptibility gene mutation (*BRCA* mutation) (germline or somatic) before LYNPARZA capsules treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test methodology.

- LYNPARZA should not be given in combination with other anti-cancer therapy.

- Grapefruit, star fruit, pomegranate and Seville oranges or their juices which are known to inhibit CYP3A should not be consumed while taking LYNPARZA (see DRUG INTERACTIONS).

Recommended Total Daily Dose for Capsule

The recommended total daily dose of LYNPARZA capsules is 800 mg, taken as eight 50 mg capsules orally twice daily.

LYNPARZA capsules should be taken on an empty stomach (at least 1 hour after a meal) and patients should refrain from eating for up to 2 hours.

Capsules should be swallowed whole and not chewed, crushed, dissolved, or divided.

Patients should start treatment with LYNPARZA no later than 8 weeks after completion of their final dose of the platinum-containing regimen. Patients should have recovered from prior hematologic toxicities prior to starting LYNPARZA therapy (hemoglobin, platelet, and neutrophil levels should be ≤ CTCAE grade 1) (see ADVERSE REACTIONS).

It is recommended that LYNPARZA treatment be continued until progression of the underlying disease.

Dose adjustment

For Adverse Events

Treatment may be interrupted to manage adverse events and dose reductions can be considered. The recommended reduced total daily dose of LYNPARZA (olaparib capsules) is 400 mg. If a further dose reduction is required, the recommended reduced total daily dose for LYNPARZA (olaparib capsules) is 200 mg.

For Co-administration with CYP3A Inhibitors

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended reduced total daily dose of LYNPARZA (olaparib capsules) is 300 mg. If a moderate CYP3A inhibitor must be co-administered, the recommended reduced total daily dose of LYNPARZA (olaparib capsules) is 400 mg (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

For Patients with Renal Impairment

For patients with moderate renal impairment (creatinine clearance 31 - 50 mL/min) the recommended reduced total daily dose of LYNPARZA (olaparib capsules) is 600 mg. LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 mL/min) as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51-80 mL/min) with no dose adjustment (see ACTION AND CLINICAL PHARMACOLOGY).

Reduced Total Daily Dose for Capsule

Adult dose 600 mg: take six 50 mg capsules twice a day.

Adult dose 400 mg: take four 50 mg capsules twice a day.

Adult dose 300 mg: take three 50 mg capsules twice a day.

Adult dose 200 mg: take two 50 mg capsules twice a day.

Table 5 Comparison of LYNPARZA capsules and tablets information

Dosage Formulation, Strength, and Packaging	**Capsules 50 mg** Available in 190 ml bottles, supplied in a carton of four bottles.	**Tablets 150 mg** Available in 110 ml and 190 ml bottles.	**Tablets 100 mg** Available in 110 ml and 190 ml bottles.
Recommended Dosage*	400 mg twice daily Morning: 8 x  Evening: 8 x  Total Daily Dosage: 800 mg	300 mg twice daily Morning: 2 x  Evening: 2 x  Total Daily Dosage: 600 mg	**Only to be used for tablet dose reductions** 
Dose adjustments	Dose reductions are achieved using fewer 50 mg capsules	Dose reductions are achieved using 100 mg and 150 mg tablets	
Adverse reactions	**Initial reduced dosage:** 200 mg BID (total daily dosage: 400 mg) **For further reductions use:** 100 mg BID (total daily dosage: 200 mg)	**Initial reduced dosage:** 250 mg BID (total daily dosage: 500 mg) **For further reductions use:** 200 mg BID (total daily dosage: 400 mg)	
Co-administration with CYP3A4 inhibitors	**Strong inhibitor:** 150 mg BID (total daily dosage: 300 mg) **Moderate inhibitor:** 200 mg BID (total daily dosage: 400 mg)	**Strong inhibitor:** 100 mg BID (total daily dosage: 200 mg) **Moderate inhibitor:** 150 mg BID (total daily dosage: 300 mg)	
Moderate renal impairment	300 mg BID (total daily dosage: 600 mg)	200 mg BID (total daily dosage: 400 mg)	

* Images of the formulations are representations only and are not to scale
BID twice daily

Missed Dose

If a patient misses a dose of LYNPARZA, they should take their next normal dose at its scheduled time. The patient should not take a double dose to make up for forgotten capsules.

Special patient populations

Pediatric (<18 years): LYNPARZA is not indicated for use in pediatric patients, as safety and efficacy of LYNPARZA in children and adolescents have not been established.

Geriatric (>65 years): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 65 or over.

Patients with Hepatic Impairment: LYNPARZA can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment. LYNPARZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C) as safety and pharmacokinetics have not been studied in these patients (see ACTION AND CLINICAL PHARMACOLOGY).

OVERDOSAGE

There is a risk of LYNPARZA (olaparib) overdose due to medication errors from confusion related to differences in posology and dosing of the capsule and tablet formulation.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LYNPARZA (olaparib) is a selective inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2 and PARP-3). Olaparib has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth *in vivo*. Cell lines or animal tumour models deficient in BRCA function or with other homologous recombination deficiencies (HRD), are particularly sensitive to treatment with olaparib.

Pharmacodynamics

PARP enzymes are required for the efficient repair of DNA single strand breaks (SSB) and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies via poly(ADP) ribose chains (PAR) and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it disrupts 1) PAR formation, and 2) the dissociation of PARP from the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. Typically homologous recombination repair (HRR), which requires functional *BRCA*1 and 2 genes, is effective at repairing these DNA DSBs in an error- free manner. In the absence of functional BRCA 1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability reaches insupportable levels and results in cancer cell death (see DETAILED PHARMACOLOGY).

Effect on the QT interval

There is no clinically relevant effect of olaparib on cardiac repolarisation (as evaluated by an effect on the QT interval) following 300 mg tablet twice daily multiple dosing of olaparib in 109 patients.

Pharmacokinetics

The pharmacokinetics of olaparib, following 400 mg single and BID capsule administration in patients with advanced solid tumours, are characterised in Table 6.

Table 6 Summary of olaparib plasma pharmacokinetic parameters following 400 mg single and BID capsule administration in patients with advanced solid tumours

	Single Dose	**Multiple Dose[a]**	**Multiple Dose[a]**
Parameters	Day 1	Day 1	Day 29
N	6	18	17
t_{max} (h) median (min-max)	1.25 (1.0 – 8.0)	NC	NC
C_{max} (µg/mL) Geometric mean (CV%) (min-max)	5.67 (47) (2.72-8.93)	5.73 (40) (3.06 – 13.9)	6.36 (34) (3.88 – 13.3)
C_{min} (µg/mL) Geometric mean (CV%) (min-max)	NA	NA	1.04 (137) (0.23 – 8.49)
$AUC_{(0-12)}$ (µg*h/mL) Geometric mean (CV%) (min-max)	NC	28.8 (67) (8.95 - 110)	41.5 (63) (18.7 - 147)
AUC_{inf} (µg*h/mL) Geometric mean (CV%) (min-max)	57.9 (78) (18.3-99.7)	NC	NA
$t_{1/2}$ (h) Mean (SD) (min-max)	11.9 (4.82) (7.15-17.8)	NC	NA
CL/F (L/h) Mean (SD) (min-max)	8.64 (7.11) (4.01-21.9)	NC	NC
V_z/F (L) Mean (SD) (min-max)	166.8 (196.4) (41.4-561)	NC	NA

PK parameters on Day 1 were derived using non-compartmental analysis from intensive PK sampling. Steady state (Day 29) PK parameters were derived using population PK analysis of data from sparse PK sampling.

[a]This group consisted of 5 patients with a primary tumour location of breast and 13 patients with a primary tumour location of ovary. All patients had confirmed *BRCA* 1/2 mutation.

Abbreviations: BID = twice daily; t_{max} = Time to maximum plasma drug concentration; C_{max} = Maximum plasma concentration; C_{min} = Minimum plasma concentration; $AUC_{(0-12)}$ = AUC from zero to 12 hours post-dose;

AUC_{inf} = Area under plasma concentration time curve extrapolated to infinity; $t_{1/2}$ = terminal plasma elimination half-life; CL/F = Apparent clearance; V_z/F = Apparent volume of distribution during the terminal phase; CV% = Coefficient of variation; SD = Standard deviation; NA = Not Applicable; NC = Not calculated in the study

In vitro, human plasma protein binding of olaparib was dose-dependent; the fraction bound was approximately 91% at 1 µg/mL, reducing to 82% at 10 µg/mL and to 70% at 40 µg/mL. In solutions of purified proteins, the olaparib fraction bound to albumin was approximately 56%, which was independent of olaparib concentrations. Using the same assay, the fraction bound to alpha-1 acid glycoprotein was 29% at 10 µg/mL with a trend of decreased binding at higher concentrations.

Absorption: The absolute bioavailability of olaparib is unknown. Following a single oral administration of olaparib (capsule formulation), absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. Inter-individual variability of olaparib exposure is high and the exposure appears to increase less than proportionally with dose over the range from 100 mg to 400 mg. On multiple dosing, steady state exposures are achieved within 3 to 4 days and accumulation ratio is approximately 1.4.

Co-administration with a high fat meal slowed the rate of absorption (median t_{max} delayed by 2 hours) and increased the extent of absorption of olaparib (mean AUC increased by approximately 20%).

LYNPARZA (olaparib) is available as a tablet and capsule formulation. The oral bioavailability of the tablet formulation is higher than the capsule formulation (see DOSAGE AND ADMINISTRATION, Dosing Considerations for Capsule). 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 300 mg tablet dose were 42.1 µg*h/mL (n=204) and 5.8 µg/mL (n=204), respectively, and the steady state geometric mean AUC and C_{max} 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 such that the steady state clearance decreased by 15% after multiple dosing.

Distribution: Following a single oral dose of 400 mg (capsule formulation), the mean apparent volume of distribution (± standard deviation [SD]) of olaparib was 167 ± 196 L. *In vitro*, human plasma protein binding of olaparib is approximately 82% at clinically relevant concentrations of 10 µg/mL. The distribution of olaparib in the central nervous system has not been studied in humans. In rat and mouse quantitative whole body autoradiography studies, olaparib-related radioactivity was below the limit of quantification in the brain and spinal cord after oral dosing of ^{14}C-olaparib (see DETAILED PHARMACOLOGY). Olaparib is a substrate of MDR1.

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

Following oral dosing of 14C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively). The metabolism of olaparib is extensive with the main site of metabolism being the piperazine and fluorobenzyl ring structures. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing <1% of the dosed material. A ring-open piperazin-3-ol moiety, and two mono-oxygenated metabolites (each~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro,* however, PBPK simulations suggest this is not of clinical importance. Based on evaluation using enzyme activity, olaparib was not an inducer of CYP2C9 or 2C19. *In vitro,* olaparib is a substrate of and inhibits the efflux transporter P-gp (IC50 = 76µM), however, this is unlikely to be of clinical significance.

Olaparib caused a slight increase in CYP1A2 mRNA without apparent increase in enzyme activity which may suggest any clinical change will be small.

In vitro, data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2, is a weak inhibitor of BCRP and not an inhibitor of OATP1B3, OAT1 or MRP2.

Excretion: Following a single oral 400 mg capsule dose of olaparib, the mean (± standard deviation) plasma terminal half-life was 11.9 ± 4.8 hours and apparent plasma clearance was 8.6 ± 7.1 L/h.

Following a single oral capsule dose of ^{14}C-olaparib, approximately 86% of the dosed radioactivity was recovered within a 7 day collection period, 44% via the urine and 42% via the faeces. Unchanged olaparib was the major component found in both urine and faeces (15% and 6% of the dose respectively).

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of olaparib in pediatric patients.

Geriatrics: There are limited data in patients aged 65 and over. A population analysis of the available data has found no relationship between olaparib plasma concentrations and patient age.

Gender: In population based PK analyses, gender was not a significant covariate.

Race: In population based PK analyses, patient race (including White and Japanese patients) was not a significant covariate.

Hepatic impairment: In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild hepatic impairment (Child-Pugh classification A) mean AUC increased by 15% and mean C_{max} by 13% and to patients with moderate hepatic impairment (Child-Pugh classification B) mean AUC increased by 8% and mean C_{max} decreased by 13% compared with patients with normal hepatic function. No LYNPARZA dose adjustment is required in patients with mild or moderate hepatic impairment (see DOSING AND ADMINISTRATION). LYNPARZA has not been studied in patients with severe hepatic impairment (Child-Pugh classification C). Capsule and tablet formulations are not bioequivalent and are not interchangeable.

Renal impairment: In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild renal impairment (creatinine clearance 51-80 mL/min), mean AUC increased by 24% and mean C_{max} by 15% compared with patients with normal renal function. Following a single oral 300 mg dose of olaparib (tablet formulation) to patients with moderate renal impairment (creatinine clearance 31-50 mL/min), mean AUC increased by 44% and mean C_{max} by 26% compared with patients with normal renal function (see DOSAGE AND ADMINISTRATION). Capsule and tablet formulations are not bioequivalent and are not interchangeable.

Weight: There are no data in obese (BMI >30 kg/m^2) or underweight (BMI <18 kg/m^2) patients. A population pharmacokinetic analysis of the available data has found no evidence that patient weight affects olaparib plasma concentrations.

STORAGE AND STABILITY

Store between 2 - 8°C. Instruct patients that they can store LYNPARZA capsules at room temperature (not exceeding 25°C) for up to 3 months if needed. The capsules must be discarded after this period. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

LYNPARZA (olaparib) 50 mg is a white, opaque, hard capsule, marked in black ink with "OLAPARIB 50 mg" on the cap and the AstraZeneca logo on the body.

Composition

Each capsule contains 50 mg of olaparib. Each capsule also contains the following nonmedicinal ingredients: gellan gum (E418), hypromellose, iron oxide black (E172), lauroyl macrogol-32 glycerides, potassium acetate, shellac, titanium dioxide (E171).

Packaging

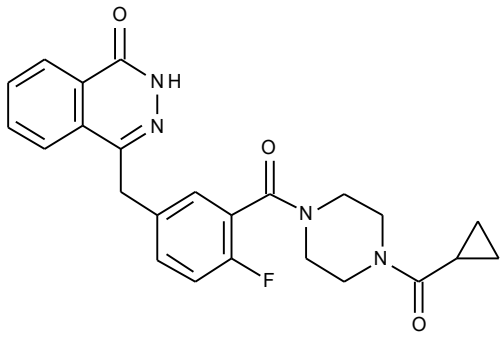
LYNPARZA is available in HDPE plastic bottles, with a child-resistant closure, containing 112 capsules.

LYNPARZA (olaparib capsules) is also available as 100 mg and 150 mg olaparib tablets. Refer to the LYNPARZA tablets Product Monograph for specific dosing information. 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. Therefore, the specific dosage recommendations for each formulation should be followed.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	Olaparib
Chemical Name:	4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one
Code Name:	AZD2281; KU-0059436
Molecular Formula and Molecular Mass:	$C_{24}H_{23}FN_4O_3$ 434.46
Structural Formula:	
Physicochemical Properties:	Olaparib is a crystalline powder and is classified as poorly soluble. The melting point (defined as the temperature onset) of olaparib is at 206°C as measured by differential scanning calorimetry. The octanol/water (pH =7.4) partition coefficient: Log D =1.49. Olaparib is achiral.

CLINICAL TRIALS

Platinum-Sensitive Relapsed (PSR) Ovarian Cancer

Study demographics and trial design

The safety and efficacy of LYNPARZA (olaparib capsule) as a maintenance therapy in the treatment of PSR high grade serous ovarian, fallopian tube and primary peritoneal cancer patients, following treatment with two or more platinum containing regimens, was studied in a Phase II randomised, double blind, placebo controlled trial (Study 19). The study compared the efficacy of LYNPARZA capsule dose of 400 mg twice daily maintenance treatment with placebo maintenance treatment. The treatments were to be administered until disease progression. The study randomised 265 PSR ovarian cancer patients (136 patients to the LYNPARZA arm and 129 patients to the placebo arm). Only PSR patients who were in complete or partial response following completion of last platinum based chemotherapy and whose disease had recurred >6 months after completion of the penultimate platinum based chemotherapy were enrolled. Patients could not have received prior LYNPARZA or other

PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomization.

The primary endpoint was progression free survival (PFS) based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included overall survival (OS), disease control rate (DCR) defined as confirmed CR/PR + stable disease (SD), health related quality of life (HRQoL), and disease related symptoms.

Patients in the LYNPARZA group continued to receive treatment longer than those in the placebo group. A total of 54 (39.7%) patients received treatment for >12 months in the LYNPARZA group compared with 14 (10.9%) patients in the placebo group. A total of 32 (23.5%) patients received treatment for ≥ 2 years in the olaparib group compared with 5 (3.9%) patients in the placebo group. A total of 18 (13.2%) patients received treatment for ≥5 years in the olaparib group compared with 1 (0.8%) patient in the placebo group. The median total treatment duration in all patients was 8.7 months in the LYNPARZA group and 4.6 months for placebo.

BRCA status was determined in 96% (254 out of 265 patients) of the overall patient population. *BRCA* mutation (germline and/or somatic) was detected in 136 patients; 74 were in the LYNPARZA group and 62 were in the placebo group.

Demographic and baseline patient characteristics were generally well balanced between treatment groups for all patients and are summarized in Table 7.

Table 7 Demographic and patient characteristics at baseline for the overall population and the BRCA-mutated subgroup: Study 19

	All patients		***BRCAm***	
	LYNPARZA 400 mg twice daily N=136	**Placebo N=129**	**LYNPARZA 400 mg twice daily N=74**	**Placebo N=62**
Age (years)				
Mean (standard deviation)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)
Median (range)	58.0 (21 to 89)	59.0 (33 to 84)	57.5 (38 to 89)	55.0 (33 to 84)
Age group, n (%)				
<50 years	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)
≥50 to <65 years	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)
≥65 years	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)
Race, n (%)				
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)
Black or African American	2 (1.5)	1 (0.8)	2 (2.7)	0

Table 7 Demographic and patient characteristics at baseline for the overall population and the BRCA-mutated subgroup: Study 19

	All patients		***BRCAm***	
	LYNPARZA 400 mg twice daily N=136	**Placebo N=129**	**LYNPARZA 400 mg twice daily N=74**	**Placebo N=62**
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0
ECOG PS, n (%)				
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)
(2) In bed ≤50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)
Primary tumour location				
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)
Fallopian tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)
Other	0	1 (0.8)[a]	0	0
Tumour grade				
Well differentiated (G1)	0	0	0	0
Moderately differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)
Poorly differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)
Number of previous chemotherapy regimens				
Mean	3	3	3.26	2.95
Median (range)	3 (2-11)	3 (2-8)	3 (2-11)	3 (2-8)
Number of previous platinum-containing chemotherapies				
Mean	2.6	2.6	2.76	2.47
Median (range)	2 (2-7)	2 (2-6)	2 (2-7)	2 (2-6)

[a] Other – Fimbria

BRCAm = Breast cancer susceptibility gene-mutated; ECOG PS = Eastern Cooperative Oncology Group performance status; N = Total number of patients.

BRCAm subgroup included patients with germline and/or somatic *BRCA* mutation.

Study 19 results

The study met its primary objective. Patients who received LYNPARZA maintenance monotherapy had a statistically significant and clinically relevant PFS improvement compared with patients who received placebo in the overall population (hazard ratio [HR] 0.35; 95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo). At the final analysis (data cut off [DCO] 9 May 2016) for OS at 79% maturity, the HR comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; p=0.02138 [did not meet pre-specified significance level of < 0.0095]; median 29.8 months olaparib versus 27.8 months placebo).

Subgroup analysis identified patients with *BRCA*-mutated ovarian cancer as the subgroup that derived the greatest clinical benefit from LYNPARZA maintenance monotherapy. There were no multiplicity strategies in place for the sub-group analyses.

In *BRCA*-mutated patients, there was a statistically significant improvement in PFS (see Table 8). The median PFS improvement was 6.9 months over placebo (HR 0.18; 95% CI 0.10-0.31; p<0.00001; median 11.2 months vs 4.3 months). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0.62 (95% CI 0.42-0.93; p=0.02140; median 34.9 months versus 30.2 months) (see Table 8). In the olaparib-treated group, 28.4% of patients remained on treatment for ≥2 years and 14.9% for ≥5 years. In the placebo-treated group, 8.1% of patients remained on treatment for ≥2 years and 1.6% for ≥5 years.

Within the *BRCA*-mutated population, the disease control rate at 24 weeks was 57% and 24% for patients in the LYNPARZA and placebo groups, respectively.

The key efficacy findings from Study 19 for *BRCA*-mutated patients are presented in Table 8, and Figure 1.

Table 8 Summary of key efficacy findings for patients with BRCA mutated PSR ovarian cancer in Study 19

PFS – DCO 30 June 2010					
	N (events/patients)[a] (%)	**Median PFS (months)**	**HR[b]**	**95% CI**	**p-value**
Olaparib 400 mg twice daily	26/74 (35)	11.2	0.18	0.10-0.31	<0.00001
Placebo	46/62 (74)	4.3			
OS (79% maturity) – DCO 09 May 2016					
	N	**Median OS (months)**	**HR[a]**	**95% CI**	**p-value***
Olaparib 400 mg twice daily	49/74 (66)	34.9	0.62	0.42-0.93	0.02140
Placebo [c]	50/62 (81)	30.2			

* There were no multiplicity strategies in place for the sub-group analyses.

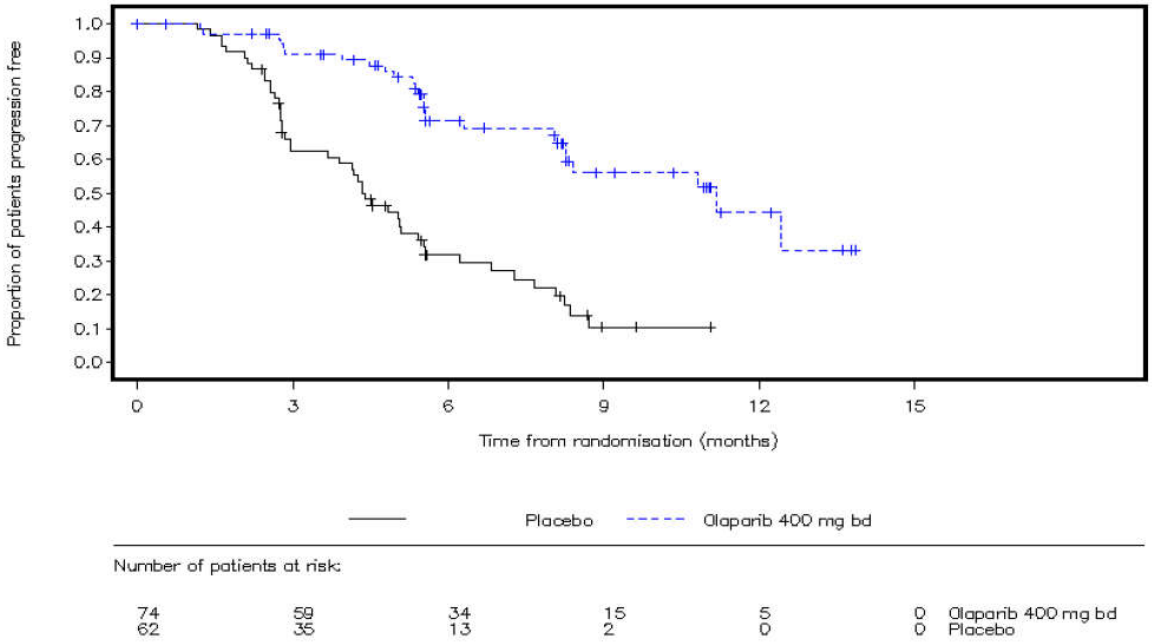
[a] Number of events/number of randomised patients

[b] HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for randomised treatment (ethnic descent, platinum sensitivity and response to final platinum therapy).

[c] Approximately a quarter of placebo treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.

OS = Overall survival; PFS = Progression-free survival; CI = Confidence interval; DCO = Data cut off.

Figure 1 Study 19: Kaplan Meier plot of PFS in BRCA mutated patients (investigator assessment)



Olaparib 400 mg bd = number of patients at risk in the olaparib group; Placebo = number of patients at risk in the placebo group.

In Study 19, 18 patients were identified with only somatic *BRCA* mutations (i.e., having mutations in the tumour but with a wildtype germline *BRCA* status). There is limited efficacy data for these patients.

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

There are 17 known members of the PARP family of proteins and olaparib has been demonstrated to selectively inhibit PARP-1, PARP-2 and PARP 3. Only PARP-1 and PARP-2 are associated with the repair of DNA single strand breaks (SSBs) and while PARP-1 is the main family member involved in the repair of DNA SSBs, PARP-2 still has the ability to bind to DNA and compensate for PARP-1 activity in this regard. PARP-2 has also been shown to play an essential role in hematopoietic stem/progenitor cell survival under steady-state conditions and in response to stress. PARP-3 does not have a known role in DNA SSB repair but rather accelerates DNA DSB repair through non-homologous end joining. PARP-1 has also been implicated in the repair of DNA DSBs and this activity may contribute directly to the mechanism of action of PARP-1 inhibitors.

LYNPARZA demonstrates single agent activity in *BRCA* mutated tumours which results in synthetic lethality. Synthetic lethality reflects the targeting of a PARP dependency, which

results from the tumour's loss of error-free homologous recombination repair (HRR) capability as a consequence of *BRCA*1 or *BRCA*2 mutations. An analysis of a panel of cancer cell lines treated with olaparib revealed a sensitivity in cells containing *BRCA* mutations or other HRR defects.

In vivo, *BRCA*-deficient orthotopic and xenograft animal models treated with olaparib resulted in tumour regression and/or tumour growth delay. Additionally, a PK/PD/efficacy relationship has been established in *BRCA* deficient models which suggested that efficacy required either the IC_{50} of tumour PARP to be exceeded for 13 hours or the IC_{90} to be achieved for 6 hours. Modelling of poly ADP ribosylation (PAR) inhibition and DNA SSB formation further suggests a significant increase in SSBs occurring only when the IC_{90} of PAR inhibition occurred. This model predicts that only by maintaining significant (>90%) inhibition of PAR levels can a large increase in SSB be generated that would translate into tumour cell kill. Consistent with this, the clinical activity of olaparib appears to be associated with doses that maintain the unbound steady state trough concentration above the IC_{90} for PARP inhibition.

A correlation has been identified between platinum sensitivity and olaparib sensitivity in ovarian and breast cancer preclinical models. In addition, *in vivo* data in *BRCA* knock-out (KO) models have also demonstrated improved tumour control and overall survival benefit in animals treated with increasing continuous once daily maintenance dosing following platinum treatment.

Secondary Pharmacodynamics

Olaparib was inactive in a panel of human recombinant voltage-gated cardiac ion channels *in vitro* at up to a maximum concentration of 31.6 μM.

Safety Pharmacology

In a rat study assessing the potential for effects on the central, peripheral and autonomic nervous systems (Irwin Study), single oral dosing of olaparib to male rats at up to 250 mg/kg produced no behavioural or physiological changes. The dose levels used in this study would have been associated with maximal total exposures that were approximately 6-fold in excess of those seen clinically. Furthermore, in the repeat dose toxicity studies in rats and dogs following dosing for up to 6 months, there was no evidence of any adverse signs suggestive of effects on the nervous system. The mean total systemic exposures (C_{max}) associated with the dose levels used in the rat or dog 6-month repeat dose studies were approximately 2- and 3-fold below those achieved clinically.

In studies assessing the potential for effects on cardiovascular and respiratory parameters, increases in heart rate and changes in all respiratory parameters (peak inspiratory and expiratory flow, tidal volume, minute volume and rate of respiration) were seen at the highest dose examined (15 mg/kg) following intravenous administration to anaesthetised dogs.

In the hERG-encoded potassium channel *in vitro* assay, olaparib had an IC_{50} of 226 μM, which was >115-fold higher than the human mean unbound C_{max} (1.95 μM) at the clinical dose.

Pharmacokinetics

Animal

The distribution of radioactivity in rats was investigated by quantitative whole body autoradiography (QWBA). One hour after administration of a single oral dose of [^{14}C]-olaparib to male Lister hooded rats (15 mg/kg), radioactivity was widely distributed. The highest concentrations of radioactivity were detected in a number of glandular tissues (eg adrenal, thyroid, Harderian gland, prostate and spleen), the mucosa of the upper and lower gastrointestinal (GI) tract, the liver, the bladder and the kidney. Distribution throughout the GI tract was typical of an oral drug. Radioactivity was below the limit of quantification in the brain and spinal cord and below the concentration in blood in many tissues. By 4 hours after dosing, concentrations of radioactivity had decreased in most tissue although the uveal tract, prostate and seminal vesicles were notable exceptions; concentrations of radioactivity also increased in parts of the GI tract at this time although they decreased in liver and kidney. By one day post dose, radioactivity was below the limit of quantification in the majority of tissues although it was still present at low levels in a small number of tissues including parts of the GI tract, excretory organs, pigmented skin and uveal tract. By 7 days after dosing, radioactivity was detectable by QWBA at low levels in only liver and uveal tract. Radioactivity was undetectable by QWBA in any tissues by 28 days after dosing although very low levels were detected in whole eye by liquid scintillation counting. Any binding of drug related material to melanin rich tissues (eg, the uveal tract, pigmented skin) appeared to be of relatively short duration with levels of radioactivity in these tissues at 3 days after dosing being similar to those in the excretory organs. The distribution of radioactivity was similar for male and female animals although higher concentrations of radioactivity were present in many tissues of female animals than in the tissues of male animals at equivalent times.

Single oral doses of [^{14}C]-olaparib to female nude mice bearing HTC-116 human colorectal tumours produced a similar distribution of radioactivity to that in rat. Additionally, radioactivity was present in tumour at higher concentrations than blood and was retained in tumour longer than in blood.

TOXICOLOGY

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with olaparib. However, the absence of PARP in genetically engineered mouse models leads to an increased risk of spontaneous and induced carcinogenesis as compared to PARP wild-type counterparts. The significance of this finding in patients is not clear.

In genotoxicity studies, olaparib did not demonstrate mutagenic potential in the bacterial reverse mutation (Ames) test, but was clastogenic *in vitro* in a chromosome aberration test and induced micronuclei in the bone marrow of rats following oral dosing for 2 days. This clastogenicity was consistent with genomic instability resulting from the primary pharmacology of olaparib.

Repeat dose toxicity

In rats, repeated daily oral dosing of olaparib at dose levels up to 40 mg/kg/day for 1 month or 15 (in females) or 30 (in males) mg/kg/day for up to 6 months was associated with reductions in body weight, body weight gain and/or food consumption. These dose levels in the rat studies were associated with mean total exposures approximately 3-fold below those achieved clinically. Oral dosing of dogs with olaparib at 50 mg/kg/day for up to 7 days was associated with adverse clinical signs, body weight loss and inappetence, requiring 1 dog to be killed prematurely on Day 5. The mean total exposure to olaparib in these dogs was approximately the same as that achieved in humans at the clinical dose of 400 mg twice a day. Based on these findings, lower dose levels of olaparib were selected for the 1-month (2.5, 5 and 15 mg/kg/day) and 6-month (1, 3, and 10 mg/kg/day) repeat dose dog studies. These dose levels of olaparib were well tolerated, with no adverse effects on food consumption or body weight, and associated with mean total exposures approximately 3-fold below those seen at the clinical dose (400 mg twice daily).

In both species, the principal target organ for toxicity following repeat dosing for up to 6 months was the bone marrow, with associated changes in peripheral hematology parameters, although steady state exposures at the highest dose levels of olaparib used in the pivotal 1 and 6 month repeat dose rat and dog toxicity studies were notably lower than those achieved in humans at the 400 mg twice daily clinical dose.

In rats, reductions in red blood cell parameters and white blood cell, neutrophil and/or lymphocyte counts, and increases or decreases in reticulocyte and platelet counts were seen. These changes were generally mild in severity, although more marked decreases in reticulocyte and platelet counts were seen at the high doses of 100 or 200 mg/kg/day used in the 7 day study. In rats, the hematology changes were associated with increases in the erythropoietic and/or myelopoietic cell populations within the bone marrow, and with increases in splenic hemopoiesis, hepatocyte pigmentation (hemosiderin) and/or thymic atrophy. The changes were more notable in female rats as a result of the higher systemic exposures in this sex. The mean total exposures to olaparib, following once daily dosing for 7 days at 100 or 200 mg/kg/day in rats, were approximately 3 and 6 folds, respectively, greater than those achieved at the clinic dose (400 mg twice daily). Full reversal of compound-related changes in rats was evident following withdrawal of treatment.

In dogs, reductions in red blood cell parameters and white blood cell, neutrophil, lymphocyte, reticulocyte and/or and platelet counts were observed following dosing at 15 mg/kg/day for up to 1 month, and were associated with bone marrow atrophy and with an increase in the myeloid/erythroid (M:E) ratio in the bone marrow smear. Decreases in red and white blood cells and platelets were seen following dosing of dogs at 10 mg/kg/day for 6 months, but were not associated with any microscopic changes in the bone marrow. The mean total exposures in dogs at these dose levels were approximately 3-fold below those achieved in humans at the clinical dose of 400 mg twice daily. Full reversal of compound-related bone marrow changes, and partial reversal of the hematology changes was seen following a 1 month recovery period.

Studies using human donor and rat bone marrow cells also showed that direct exposure to olaparib can result in toxicity to bone marrow cells in *ex vivo* assays.

The effects of olaparib on bone marrow and peripheral blood may be related to the pharmacology and mechanism of action of olaparib as an inhibitor of PARP-1 and PARP-2. PARP-2 appears to play a key role in the survival of hematopoietic stem/progenitor cells under steady-state conditions and in response to stress.

Reproductive toxicology

In fertility studies conducted in rats at 0.05, 0.5 or 15 mg/kg/day, olaparib produced no adverse effects on male and female fertility. However, olaparib treatment caused an increase in early embryofetal loss when dosed to adult female rats from 14 days prior to pairing (with undosed males) through to day 6 of pregnancy at 15 mg/kg/day, a dose level that was not associated with any significant maternal toxicity. The mean total exposures at the highest dose in this study was approximately 4-fold lower than those achieved in the humans at the 400 mg twice daily clinical dose.

In embryofetal development studies in rats, oral dosing of olaparib during organogenesis caused embryofetal lethality at doses of 5 mg/kg/day and above. The mean total exposure at this dose was about 18 folds lower than those seen in humans at the 400 mg twice daily clinical dose. At a non-maternally toxic dose of 0.5 mg/kg/day, olaparib caused reductions in early embryofetal survival, decreases in fetal weights and increases in the incidence of major eye (anophthalmia, microphthalmia), fetal visceral (slightly non-uniform palate rugal pattern; additional liver lobe(s); left sided umbilical artery; slightly dilated ureter; kinked ureters and an increased incidence of severely dilated ureters), several transient skeletal minor abnormalities and/or variants (affecting cervical, thoracic and caudal vertebra, and sternebrae, hindlimb bones) and vertebrate/rib malformations (Caudal displacement of the thoracolumbar border). The mean total plasma concentration at the 0.5 mg/kg/day olaparib was approximately 190-fold lower than that achieved at the clinical dose of 400 mg twice daily in patients. At the lower dose of 0.05 mg/kg/day, there was still an increased incidence of fetal malformations including those of the eyes, skeleton and ureters such that a NOAEL for developmental toxicity was not determined. The mean total plasma exposures at the 0.05 mg/kg/day was about 240 folds lower than those seen in humans at the clinical dose of 400 mg bd.

Overall, since exposures in rats were substantially lower than those achieved in humans at the 400 mg twice daily clinical dose, this indicates that olaparib has potential to cause adverse effects in the developing fetus at therapeutic exposures. The effects on embryofetal survival seen in rats are considered to be related to PARP inhibition by olaparib, as double knock-out mice lacking both PARP-1 and PARP-2 are not viable and die at the onset of gastrulation. This demonstrates that the expression of both PARP-1 and PARP-2 are essential during early embryogenesis.

REFERENCES

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr LYNPARZA®

Olaparib Capsules

Read this carefully before you start taking LYNPARZA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LYNPARZA.

To decrease the **Risk of Medication Errors**, all patients on LYNPARZA capsules should register in the **AstraZeneca Oncology Patient Support Program**. Your healthcare professional will help you register. The program will help you take LYNPARZA capsules correctly. It will give you information and answer any questions you may have.

Serious Warnings and Precautions

- Only a doctor who has experience treating cancer should treat you with this drug.
- **Myelodysplastic Syndrome or Acute Myeloid Leukemia** is a problem with the bone marrow. You may have low red, white or platelet cell counts. This is serious and can lead to death.
- **Pneumonitis** is a lung inflammation. It makes it hard for the lungs to absorb oxygen and remove carbon dioxide. It is serious and can lead to death or require hospital treatment.
- **Risk of Medication Errors:** LYNPARZA is also available as 100 mg and 150 mg tablets. The doses of LYNPARZA capsules and tablets are not the same. Taking the wrong dose or a tablet instead of a capsule could lead to LYNPARZA not working properly or to more side effects.
- LYNPARZA can harm your unborn baby if you take it while you are pregnant.

What are LYNPARZA capsules used for?
LYNPARZA is used in adults to treat cancer of the ovaries. It can also treat some other closely related cancers. When your cancer responds to chemotherapy, LYNPARZA helps to keep that response.

LYNPARZA capsules should be used in a specific group of ovarian cancer patients. These people have mutations (changes) in certain genes called *BRCA* (known as the breast cancer gene). A test is used to determine whether you have a mutation of your *BRCA* genes.

How does LYNPARZA work?
LYNPARZA is a type of drug called a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor. In patients who have mutations (changes) in certain genes called *BRCA* (known as the breast cancer gene), LYNPARZA stops cancer cells from repairing damage to their DNA, which helps to kill the cancer cells.

What are the ingredients in LYNPARZA capsules?
Medicinal ingredients: olaparib
Non-medicinal ingredients: gellan gum, hypromellose, iron oxide black, lauroyl macrogol glycerides, potassium acetate, shellac, titanium dioxide.

LYNPARZA comes in the following dosage forms:
Capsule: 50 mg

PLEASE NOTE: LYNPARZA is also available as a 100 mg and 150 mg **tablet**.

Risk of Medication Error: The doses of LYNPARZA capsules and tablets are not the same. Taking the wrong dose or a tablet instead of a capsule could lead to LYNPARZA not working properly or to more side effects.

Do not use LYNPARZA if:
- You are allergic to olaparib or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LYNPARZA. Talk about any health conditions or problems you may have, including:
- If you have moderate or severe kidney disease.
- If you have severe liver disease.

Other warnings you should know about:
- If you are pregnant or still able to get pregnant and/or breast feed, there are specific risks you must discuss with your healthcare professional.
- Avoid becoming pregnant while taking LYNPARZA. It may harm your unborn child or make you lose the pregnancy. You should use effective methods of birth control while taking LYNPARZA. Keep using birth control for 1 month after taking your last dose of LYNPARZA. If you do become pregnant while taking LYNPARZA, tell your doctor right away.
- **For women who can get pregnant:** a pregnancy test should be done: before you start to take LYNPARZA; regularly while you are taking it; and one month after taking your last dose.
- LYNPARZA may pass into breast milk. Do not breast-feed while you are taking LYNPARZA and for one month after taking your last dose of LYNPARZA. If you are planning to breast-feed, tell your doctor.

Driving and using machines: Before you do tasks which may require special attention, wait until you know how you respond to LYNPARZA. If you feel dizzy, weak, or tired, do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
Some medicines can affect the level of LYNPARZA in your body. Also, LYNPARZA can affect the way some other medicines work. The medicines listed here may not be the only ones that could interact with LYNPARZA.

The following may interact with LYNPARZA:

- itraconazole, fluconazole - used to treat fungal infections.
- telithromycin, clarithromycin, erythromycin, ciprofloxacin - used to treat bacterial infections.
- ritonavir, nelfinavir, indinavir, saquinavir, nevirapine, cobicistat, boceprevir, telaprevir, etravirine, efavirenz, amantadine - used to treat viral infections, primarily HIV.
- rifampicin, rifapentine, rifabutin - used to treat bacterial infections, primarily tuberculosis (TB).
- phenytoin, carbamazepine, phenobarbital - used to treat seizures and epilepsy.
- St John's Wort (*Hypericum perforatum*) - an herbal remedy used mainly for depression.
- bupropion - mainly used for depression and smoking cessation.
- modafinil - used to treat a sleep disorder called narcolepsy.
- diltiazem, furosemide, valsartan, verapamil – used to treat heart conditions or high blood pressure.
- bosentan - used to treat pulmonary artery hypertension.
- statins e.g. simvastatin - used to lower blood cholesterol levels.
- glibenclamide, metformin, repaglinide - used to treat diabetes.
- ergot alkaloids - used to treat migraines and headaches.
- fentanyl - used to treat cancer pain.
- pimozide, quetiapine - used to treat mental disorders.
- cisapride, cimetidine - used to treat stomach problems.
- cyclosporine, sirolimus, tacrolimus - used to suppress the immune system.
- cisplatin - used to treat cancer.
- methotrexate - used to treat cancer, rheumatoid arthritis and psoriasis.
- midazolam - used to produce sleepiness and drowsiness.

Do not take LYNPARZA with any other drugs that treat cancer.

Do not eat or drink any products or juices containing grapefruit, star fruit, pomegranate or Seville oranges while taking LYNPARZA. They can affect the way the medicine works.

How to take LYNPARZA capsules:
Always take LYNPARZA exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.
Be sure the doctor has ordered CAPSULES for you.

- Take at least one hour after eating food. Do not eat for up to 2 hours after taking LYNPARZA capsules.
- Take at about the same time each morning and evening.
- Swallow whole. Do NOT chew, crush, dissolve or divide the capsules.
- Start taking LYNPARZA within 8 weeks of your last dose of platinum containing chemotherapy.

Recommended Total Daily Dose:
Usual adult dose 800 mg: Take eight 50 mg capsules (for a dose of 400 mg) by mouth twice a day. This is a total of 16 capsules each day, 8 in the morning and 8 in the evening. Your doctor may interrupt or reduce your dose. This may happen if you:

- have problems with your kidneys.
- are taking medicines that may interact with LYNPARZA.
- have certain side effects while taking LYNPARZA.

Your doctor will tell you how many capsules of LYNPARZA to take and it is important that you take the total recommended daily dose.

Reduced Total Daily Doses for Capsules:
Adult Daily Dose 600 mg: take as six 50 mg capsules twice a day.
Adult Daily Dose 400 mg: take as four 50 mg capsules twice a day.
Adult Daily Dose 300 mg: take as three 50 mg capsules twice a day.
Adult Daily Dose 200 mg: take as two 50 mg capsules twice a day.

Overdose:

If you think you have taken too much LYNPARZA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take LYNPARZA, take your next dose at its scheduled time. Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

What are possible side effects from using LYNPARZA?
These are not all the possible side effects you may feel when taking LYNPARZA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- headache
- feeling dizzy

- loss of appetite
- feeling tired or weak
- changes in the way food tastes
- indigestion or heartburn
- pain in the stomach area under the ribs
- rash
- itchy rash on swollen, reddened skin (dermatitis)
- cough
- shortness of breath

It is common to experience nausea and vomiting at the start of your treatment. These side effects may improve over time. Ask your doctor how to treat these side effects.

LYNPARZA can cause abnormal blood test results. Your doctor will test your blood every month for the first year of treatment and periodically thereafter. Your doctor will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (low red blood cells): Being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, weakness.		x	
Neutropenia or leukopenia (Low white blood cells: neutrophils and leukocytes): Fever or infection, fatigue, aches and pains, and flu-like symptoms.		x	
Thrombocytopenia (Low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		x	
Nausea and Vomiting: Feeling sick. Being sick or throwing up.	x		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Stomatitis (mouth sores, inflammation of the mouth) **or Mucosal Inflammation** (inflammation of the moist body surfaces): Red, sore or swollen mouth, lips, gums, nose or eyes. Ulcers can occur.	x		
Diarrhea: Severe, at least 3 loose or liquid bowel movements in a day.	x		
Myelodysplastic Syndrome or **Acute Myeloid Leukemia** (a group of diseases in which the body produces large numbers of abnormal blood cells): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool.			x
Lymphopenia (low white blood cells: lymphocytes): Get infections more easily.		x	
UNCOMMON			
Allergic reactions: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			x
Pneumonitis (lung inflammation): New or worsening shortness of breath, cough, wheezing or fever.			x

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store in the refrigerator between 2 - 8°C. You can keep LYNPARZA capsules at room temperature (up to 25°C) for up to 3 months if needed. You must throw away any unused capsules after 3 months if you store them at room temperature.
- Do not freeze.
- Do not use after the expiry date stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about LYNPARZA:

- Talk to your healthcare professional
- This Patient Medication Information leaflet provides you with the most current information at the time of printing. Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website (www.astrazeneca.ca), or by calling 1-800-668-6000.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4

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