PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr LYNPARZA®

Olaparib Tablets

Tablets, 100 mg and 150 mg, oral

Antineoplastic agent

- *LYNPARZA (olaparib) indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA wild type high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LYNPARZA, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.*
- *LYNPARZA has been issued **marketing authorization without conditions** as monotherapy for the:*
  - *Maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*
  - *Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy. Germline BRCA mutation must be confirmed before LYNPARZA treatment is initiated.*

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Date of Revision:
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Submission Control No: 210204

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

RECENT MAJOR LABEL CHANGES

INDICATION (1)	05-2018
DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment (4.2)	05-2018
WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests (7)	05-2018
WARNINGS AND PRECAUTIONS, Sexual Health (7)	05-2018
WARNINGS AND PRECAUTIONS, Pregnant Women (7.1.1)	05-2018

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- *LYNPARZA (olaparib) indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA wild type high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LYNPARZA, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.*
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

Breast Cancer

LYNPARZA (olaparib) is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy. Germline *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated.

Ovarian Cancer

LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

NOC/c

- Marketing authorization with conditions issued for ovarian cancer patients with *BRCA* wild type status was based on promising evidence of superior benefit in prolonging progression-free survival (PFS) of olaparib capsule versus placebo in a phase II trial (Study 19) in patients with *BRCA* wild type status, as assessed by investigator using RECIST 1.0. For comparative bioavailability evidence between the capsule and tablet formulation, see CLINICAL TRIALS, Comparative Bioavailability Studies.

- Marketing authorization without conditions issued for ovarian cancer patients with *BRCA* mutation was based on results from a randomized, placebo-controlled phase III trial (SOLO2) demonstrating that olaparib tablet is superior to placebo in prolonging PFS in patients with *BRCA* mutation, as assessed by investigator using RECIST 1.0 (see CLINICAL TRIALS).

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

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): There are limited clinical data in patients aged 75 years and older.

NOC/c 2 CONTRAINDICATIONS

LYNPARZA (olaparib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

NOC/c 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 tablets and capsules. To avoid medication error, prescribers should specify the formulation and dosage of LYNPARZA on each prescription. Do not substitute LYNPARZA tablets with LYNPARZA capsules on a milligram-to-milligram basis due to differences in dosing and bioavailability of each formulation (see DOSAGE AND ADMINISTRATION, Dosing Considerations for Tablet).
- LYNPARZA could cause fetal harm when administered to a pregnant woman (see WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction).

NOC/c

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations for Tablet

Non-Interchangeability between LYNPARZA Tablets and LYNPARZA Capsules
LYNPARZA (olaparib tablets) is also available as a 50 mg olaparib capsule formulation. Refer to the LYNPARZA capsules Product Monograph for specific dosing information. To avoid substitution errors and overdose, do not substitute LYNPARZA tablets with LYNPARZA capsules 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.

4.2 Recommended Dose and Dosage Adjustment

Risk of Medication Error

There is a risk of medication errors between LYNPARZA tablets and LYNPARZA capsules. In order to minimize this risk, check the bottle labels to ensure that the drug being prepared and dispensed is LYNPARZA tablets and not LYNPARZA capsules. Prescribers should specify the formulation and dosage of LYNPARZA on each prescription (see DOSAGE AND ADMINISTRATION, Dosing Considerations for Tablet; OVERDOSAGE).

Recommended Total Daily Dose for Tablet

The recommended total daily dose of LYNPARZA tablets is 600 mg, taken as two 150 mg tablets twice daily. The 100 mg tablet is available for dose reduction.

For treatment of ovarian cancer: 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 or unacceptable toxicity.

Health Canada has not authorized an indication for pediatric use (see INDICATIONS, Pediatrics).

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

Grapefruit or other similar fruit juices that are known to inhibit CYP3A should not be consumed while taking LYNPARZA (see DRUG INTERACTIONS).

Dose Adjustments

For Adverse Events: Treatment may be interrupted to manage adverse events and dose reduction can be considered. The recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 500 mg. If a further dose reduction is required, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg (see ADVERSE REACTIONS).

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 tablets) is 200 mg. If a moderate CYP3A inhibitor must be co-administered, the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 300 mg (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

For Patients with Renal Insufficiency: For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg. LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min), as safety and efficacy 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, Pharmacokinetics).

Reduced Total Daily Doses for Tablet:
Adult Dose 500 mg: take one 150 mg tablet and one 100 mg tablet twice a day.

Adult Dose 400 mg: take two 100 mg tablets twice a day.

Adult Dose 300 mg: take one 150 mg tablet twice a day.

Adult Dose 200 mg: take one 100 mg tablet twice a day.

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

Geriatrics (>65 years): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and older (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

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

4.3 Administration

LYNPARZA is for oral use.

LYNPARZA tablets should be swallowed whole and not chewed, crushed, dissolved or divided. LYNPARZA tablets can be taken with or without food.

4.4 Reconstitution

Not Applicable.

4.5 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 tablets.

5 OVERDOSAGE

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 100 mg, 150 mg	Core Colloidal silicon dioxide Copovidone Mannitol Sodium stearyl fumarate Tablet coating Hypromellose Macrogol 400 Titanium dioxide (E171) Iron oxide black (E172) (150 mg tablet only) Iron oxide yellow (E172)

Dosage Form Description
LYNPARZA (olaparib) 150 mg tablet is a green to green/grey, oval, bi-convex tablet debossed with “OP 150” on one side and plain on the reverse.

LYNPARZA (olaparib) 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet debossed with “OP 100” on one side and plain on the reverse.

Packaging
LYNPARZA is available in 60 tablets or 120 tablets per bottle for each strength in high-density polyethylene (HDPE) plastic bottles, containing desiccant, with a child-resistant closure.

LYNPARZA (olaparib tablets) is also available as a 50 mg olaparib capsule. Refer to the LYNPARZA capsules Product Monograph for specific dosing information. To avoid substitution errors and overdose, do not substitute LYNPARZA tablets with LYNPARZA capsules 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.

NOC/c

7 WARNINGS AND PRECAUTIONS

Please see the SERIOUS WARNINGS AND PRECAUTIONS Box in Section 3.

General

Interactions with other medicinal products

Co-administration of LYNPARZA (olaparib) with strong or moderate CYP3A inhibitors is not recommended (see DRUG INTERACTIONS). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

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).

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 g*BRCA*m 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. 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.

Monitoring and Laboratory Tests

BRCA Testing

For germline *BRCA*-mutated HER2-negative metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated. Germline *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 ADVERSE REACTIONS, Abnormal Laboratory Findings).

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. If MDS/AML is confirmed, discontinue LYNPARZA and treat appropriately.

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 (see WARNINGS AND PRECAUTIONS, Special Populations).

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.

Sexual Health
Reproduction
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 300 mg twice daily (see WARNINGS AND PRECAUTIONS, Special Populations; NON-CLINICAL TOXICOLOGY).

Women of childbearing potential should be advised that they must use effective contraception during LYNPARZA treatment and for one month after receiving the last dose of LYNPARZA. Male patients and their female partners of childbearing potential should be advised that they must use effective contraception during LYNPARZA treatment and for 3 months after receiving the last dose of LYNPARZA. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

7.1 Special Populations

7.1.1 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

embryofetal effects (see NON-CLINICAL TOXICOLOGY). Female partners of male patients taking LYNPARZA should also avoid pregnancy.

If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be apprised of the potential hazard to a fetus and the potential risk for loss of the pregnancy.

Contraception and pregnancy testing
Women of childbearing potential should be advised that they must use effective contraception during LYNPARZA treatment and for one month after receiving the last dose 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.

It is not known whether olaparib or its metabolites are found in seminal fluid. Male patients must use a condom during therapy and for 3 months after receiving the last dose of LYNPARZA when having sexual intercourse with a pregnant woman or with a woman of childbearing potential.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and older.

7.1.5 Hepatic insufficiency

LYNPARZA (olaparib tablets) can be administered to patients with mild hepatic impairment (Child-Pugh classification A) with no dose adjustment. LYNPARZA is not recommended for use in patients with moderate or severe hepatic impairment, as safety and efficacy have not been studied in these patients (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

7.1.6 Renal insufficiency

For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the recommended reduced total daily dose of LYNPARZA (olaparib tablets) is 400 mg (two 100 mg tablets twice daily). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min), as safety and efficacy 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, Pharmacokinetics).

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of LYNPARZA (olaparib) was evaluated in 1453 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) on LYNPARZA monotherapy (n= 1453) were nausea, fatigue, 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 commonly reported serious adverse events (in ≥1% of patients) were: anemia (3.4%), vomiting (1.3%), abdominal pain (1.2%), intestinal obstruction (1.2%), small intestinal obstruction (1.2%) and dyspnea (1.0%). Adverse events of MDS/AML and pneumonitis were reported in 1.4% and 0.6% of patients, respectively. The commonly reported AEs with CTCAE grade ≥3 severity (in ≥1% of patients) were anemia (12.9%), fatigue (5.2%), neutropenia (3.2%), vomiting (2.5%), abdominal pain (2.4%), nausea (2.0%), leukopenia (2.0%), dyspnea (1.7%), thrombocytopenia (1.7%), neutrophil count decreased (1.6%), diarrhea (1.3%), intestinal obstruction (1.2%), hemoglobin decreased (1.2%), small intestinal obstruction (1.1%), asthenia (1.0%), back pain (1.0%) and white blood cell count decreased (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 AEs leading to discontinuation of LYNPARZA was 6.3%. The frequencies of adverse reactions leading to discontinuation of LYNPARZA treatment were anemia (1.0%), neutropenia (0.4%), thrombocytopenia (0.3%), nausea (0.6%), vomiting (0.5%), fatigue (0.2%) and diarrhea (0.2%).

Hematological toxicity
Anemia and other hematological toxicities were generally CTCAE grade 1 or 2, however, there were reports of CTCAE grade 3 and higher events. 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.

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.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment of g*BRCA*m HER2-Negative Metastatic Breast Cancer (OlympiAD)

The safety of LYNPARZA (olaparib) tablets as monotherapy was evaluated in g*BRCA*m patients with HER2-negative metastatic breast cancer in the OlympiAD study. This study was a Phase III, randomized, active-controlled, open-label, multi-center study in which 296 patients received either LYNPARZA 300 mg twice daily (N=205) or a chemotherapy (capecitabine, eribulin, or vinorelbine) of the physician's choice (N=91) until disease progression or unacceptable toxicity (see CLINICAL TRIALS). The median duration of study treatment was 8.2 months in patients who received LYNPARZA and 3.4 months in patients who received chemotherapy.

Table 2 summarizes adverse drug reactions associated with LYNPARZA treatment in the OlympiAD study with frequencies reported regardless of causality.

Table 2 Adverse Drug Reactions Reported in OlympiAD (Safety Analysis Set)

System Organ Class/Preferred Term	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Blood and Lymphatic System Disorders				
Anemia[b]	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia[b]	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Leukopenia[b]	52 (25.4)	11 (5.4)	28 (30.8)	12 (13.2)
Thrombocytopenia[b]	23 (11.2)	8 (3.9)	11 (12.1)	2 (2.2)
Lymphopenia[b]	17 (8.3)	4 (2.0)	2 (2.2)	1 (1.1)
Gastrointestinal Disorders				
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Dyspepsia	16 (7.8)	0	4 (4.4)	0
Upper abdominal pain	15 (7.3)	0	5 (5.5)	1 (1.1)
Stomatitis	15 (7.3)	0	10 (11.0)	0
Gastroesophageal reflux disease	6 (2.9)	0	0	0
General Disorders and Administration Site Conditions				

Table 2 Adverse Drug Reactions Reported in OlympiAD (Safety Analysis Set)

System Organ Class/Preferred Term	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)	All CTCAE Grades n (%)	CTCAE Grades ≥3 n (%)
Fatigue (including asthenia)	75 (36.6)	8 (3.9)	33 (36.3)	1 (1.1)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Investigations				
Increase in creatinine	6 (2.9)	0	0	0
Infections and infestations				
Cystitis	3 (1.5)	0	2 (2.2)	0
Metabolism and Nutrition Disorders				
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Nervous System Disorders				
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Dysgeusia	19 (9.3)	0	6 (6.6)	0
Dizziness	16 (7.8)	0	7 (7.7)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[b]	37 (18.0)	0	6 (6.6)	0
Skin and Subcutaneous Tissue Disorders				
Rash[b]	10 (4.9)	0	5 (5.5)	0
Dermatitis[b]	1 (0.5)	0	0	0

a Physician's choice of chemotherapy consists of either capecitabine (2500 mg/m^2 oral daily, divided in 2 doses for 14 days, repeated every 21 days), eribulin (1.4 mg/m^2 IV Day 1 and Day 8, repeated every 21 days) or vinorelbine (30 mg/m^2 IV Day 1 and Day 8, repeated every 21 days).

b Anemia includes PTs of anemia, erythropenia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased, neutrophil count decreased, febrile neutropenia, neutropenic infection, and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased, and plateletcrit decreased; Lymphopenia includes PTs of lymphocyte count decreased, lymphocyte percentage decreased, lymphopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes cough and productive cough; Rash includes PTs of exfoliative rash, generalized erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic; Dermatitis includes PTs of dermatitis, dermatitis allergic, and dermatitis exfoliative.

MedDRA version 19.1; CTCAE Common Terminology Criteria for Adverse Events; PTs Preferred terms.

Dose modifications (dose reduced or dose interrupted) due to an AE of any grade occurred in 38.0% of patients receiving LYNPARZA and 41.8% of those receiving chemotherapy. The most common AEs (reported in ≥2% patients in the LYNPARZA arm) leading to dose modifications in the LYNPARZA arm vs chemotherapy arm respectively, were anemia (17.6% vs 3.3%), neutropenia (8.3% vs 16.5%), white blood count decreased (4.4% vs 4.4%), leukopenia (4.4% vs 3.3%), neutrophil count decreased (3.4% vs 7.7%), fatigue (2.9% vs 2.2%), nausea (2.9% vs 2.2%), vomiting (2.4% vs 2.2%), platelet count decreased (2.4% vs 1.1%), alanine

aminotransferase increased (2.4% vs 2.2%), aspartate aminotransferase increased (2.0% vs 2.2%), pyrexia (2.0% vs 1.1%), and thrombocytopenia (2.0% vs 1.1%).

The most common serious adverse reaction reported was anemia (2.4% olaparib vs 2.2% chemotherapy). The following serious ADRs were reported in one patient each: dermatitis allergic, neutrophil count decreased and platelet count decreased.

The proportion of patients who permanently discontinued LYNPARZA due to adverse events was 4.9% in the LYNPARZA arm compared with 7.7% in the chemotherapy arm. Anemia and platelet count decrease were the only adverse reactions leading to discontinuation of LYNPARZA in more than one patient (LYNPARZA: 4/205 and 2/205, respectively vs chemotherapy: 2/91 and 0/91, respectively).

Treatment of Ovarian Cancer (SOLO2 Study)

The SOLO2 study is a randomized, phase III, double-blind, placebo-controlled trial of LYNPARZA 300 mg twice daily (2 x 150 mg tablets) maintenance monotherapy in patients with platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer (n=295 [n=196 on LYNPARZA and n=99 on placebo]). The total median exposure to study treatment was 19.4 months in the LYNPARZA group and 5.6 months in the placebo group. Table 3 summarizes adverse drug reactions associated with LYNPARZA tablet with frequencies reported regardless of causality.

Table 3 Adverse Drug Reactions Reported in SOLO2 (Safety Analysis Set)

	LYNPARZA 300 mg tablets twice daily N = 195		Placebo N = 99	
System Organ Class/ Preferred Term	**All Grades n (%)**	**CTCAE ≥Grade 3 n (%)**	**All Grades n (%)**	**CTCAE ≥Grade 3 n (%)**
Blood and Lymphatic System Disorders				
Anemia[a]	85 (43.6)	38 (19.5)	8 (8.1)	2 (2.0)
Neutropenia[a]	38 (19.5)	10 (5.1)	6 (6.1)	4 (4.0)
Thrombocytopenia[a]	27 (13.8)	2 (1.0)	3 (3.0)	1 (1.0)
Leukopenia[a]	31 (15.9)	5 (2.6)	2 (2.0)	0
Lymphopenia[a]	2 (1.0)	1 (0.5)	0	0
Gastrointestinal Disorders				
Nausea	148 (75.9)	5 (2.6)	33 (33.3)	0
Vomiting	73 (37.4)	5 (2.6)	19 (19.2)	1 (1.0)
Diarrhea	64 (32.8)	2 (1.0)	20 (20.2)	0
Dyspepsia	22 (11.3)	0	8 (8.1)	0
Upper Abdominal Pain	21 (10.8)	0	12 (12.1)	0
Stomatitis	20 (10.3)	2 (1.0)	6 (6.1)	0
General Disorders and Administration Site Conditions				

Table 3 Adverse Drug Reactions Reported in SOLO2 (Safety Analysis Set)

System Organ Class/ Preferred Term	LYNPARZA 300 mg tablets twice daily N = 195		Placebo N = 99	
	All Grades n (%)	CTCAE ≥Grade 3 n (%)	All Grades n (%)	CTCAE ≥Grade 3 n (%)
Fatigue (including asthenia)	128 (65.6)	8 (4.1)	39 (39.4)	2 (2.0)
Investigations				
Increase in creatinine	21 (10.8)	1 (0.5)	1 (1.0)	0
Mean corpuscular volume elevation	1 (0.5)	0	0	0
Metabolism and nutrition disorders				
Decreased appetite	43 (22.1)	0	11 (11.1)	0
Nervous system disorders				
Headache	49 (25.1)	1 (0.5)	13 (13.1)	0
Dysgeusia	52 (26.7)	0	7 (7.1)	0
Dizziness	26 (13.3)	1 (0.5)	5 (5.1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	35 (17.9)	1 (0.5)	5 (5.1)	0
Skin and Subcutaneous Tissue Disorders				
Rash[a]	16 (8.2)	0	7 (7.1)	0
Dermatitis[a]	2 (1.0)	0	2 (2.0)	0

a Anemia includes preferred terms of anemia, hemoglobin decreased, red blood cell count decreased, and hematocrit decreased; Neutropenia includes preferred terms of neutropenia, granulocytopenia, granulocyte count decreased, neutrophil count decreased febrile neutropenia and neutropenic sepsis; Thrombocytopenia includes preferred terms of thrombocytopenia, platelet count decreased and plateletcrit decreased; Leukopenia includes preferred terms of leukopenia and white blood cell count decreased. Rash includes PTs of exfoliative rash, generalized erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, and rash pruritic; Dermatitis includes PTs of dermatitis, dermatitis allergic, and dermatitis exfoliative.

CTCAE Common Terminology Criteria for Adverse Events; PTs Preferred terms.

The most commonly reported AEs that led to dose modification in the LYNPARZA arm vs. placebo arm were anemia (22.1% vs. 0%), vomiting (7.2% vs.1.0%), nausea (5.6% vs. 3.0%), neutropenia (4.6% vs. 3.0%), fatigue (4.6% vs. 0%), asthenia (4.1% vs. 1.0%), leukopenia (3.6% vs. 0%), abdominal pain (3.1% vs. 2.0%), diarrhea (3.1% vs. 0%), thrombocytopenia (3.1% vs. 1.0%), dyspnea (2.1% vs. 0%), neutrophil count decreased (2.1% vs. 0%) and pyrexia (2.1% vs. 0%).

The most commonly reported SAEs (≥1%) in the LYNPARZA arm vs. placebo arm were anemia (3.6% vs. 0%), abdominal pain (1.5% vs. 0%), intestinal obstruction (1.5% vs. 1.0%), deep vein thrombosis (1.0% vs.1.0%) and gastric cancer (1.0% vs 0%).

Overall, based on the long-term collection of data beyond treatment discontinuation and 30 day follow-up in the SOLO-2 study (up to the data cut-off for the primary analysis), there were 4 cases of MDS/AML (2.1%) in patients randomized to LYNPARZA and 4 cases (4.0%) in patients randomized to placebo.

8.3 Less Common Clinical Trial Adverse Reactions

See Table 2 and Table 3 in ADVERSE REACTIONS, Clinical Trials Adverse Reactions.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 4 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the OlympiAD study.

Table 4 Laboratory Abnormalities Reported in OlympiAD

Laboratory Parameter[b]	LYNPARZA Tablets 300 mg bid N=205		Physician's Choice of Chemotherapy[a] N=91	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	82	17	66	3
Decrease in lymphocytes	73	21	63	3
Decrease in leukocytes	71	8	70	23
Increase in MCV[c]	71	-	33	-
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0
Increase in serum creatinine	18	0.5	9	0

[a] Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
[b] Patients were allowed to enter study with laboratory values of CTCAE Grade 1.
[c] Represents the proportion of subjects whose MCV was > upper limit of normal (ULN).
CTCAE Common Terminology Criteria for Adverse Events; MCV Mean corpuscular volume

Table 5 summarizes the frequency of laboratory abnormalities associated with LYNPARZA treatment in the SOLO2 study.

Table 5 Laboratory Abnormalities Reported in ≥25% of Patients in SOLO2

Laboratory parameter[a]	LYNPARZA Tablets 300 mg bid N=195		Placebo N=99	
	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)	CTCAE Grades 1-4 (%)	CTCAE Grades 3-4 (%)
Decrease in hemoglobin	83	17	69	0
Decrease in lymphocytes	67	11	37	1
Decrease in absolute neutrophil count	51	7	34	3
Decrease in leukocytes	69	5	48	1
Decrease in platelets	42	2	22	1
Increase in serum creatinine	44	0	29	0
Increase in mean corpuscular volume[b]	89	-	52	-

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.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not Applicable.

8.6 Post-Market Adverse Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity reactions

9 DRUG INTERACTIONS

9.1 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).

9.2 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 6 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 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 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 6 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, cyclosporine, cisapride, ergot alkaloids, fentanyl, midazolam, pimozide, sirolimus, tacrolimus, quetiapine)	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., amantadine, cimetidine, furosemide, methotrexate, metformin, cisplatin)	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.
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

9.3 Drug-Food Interactions

Co-administration with food slowed the rate (t_{max} delayed by 2.5 hours and C_{max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC treatment ratio: 1.08; 90% CI: 1.01, 1.16). Consequently, patients should take LYNPARZA without regard to food. See DOSAGE AND ADMINISTRATION, Administration.

Grapefruit, star fruit, pomegranate, Seville oranges and other similar fruits are known to inhibit CYP3A and may increase olaparib plasma concentration. Patients should avoid grapefruit and other similar fruits during LYNPARZA treatment.

9.4 Drug-Herb Interactions

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

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.6 Drug-Lifestyle 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.

NOC/c 10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

LYNPARZA (olaparib) is a selective inhibitor of human poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular functions, such as DNA transcription and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines *in vitro* and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA and non-BRCA proteins involved in the homologous recombination repair (HRR) of DNA damage and correlated with platinum response. *In vitro* studies have shown that olaparib-induced cytotoxicity involves DNA damage resulting from the inhibition of PARP enzymatic activity and increased formation of trapped PARP-DNA complexes, resulting in cancer cell death.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

The pharmacokinetics (PK) of olaparib at a single 300 mg tablet dose (two 150 mg tablets) are characterised in Table 7 by an apparent plasma clearance of ~7 L/h, an apparent volume of distribution of ~158 L and a terminal half-life of 15 hours. On multiple dosing, an AUC accumulation ratio of 1.8 was observed and PK appeared to be time-dependent to a small extent.

Table 7 LYNPARZA (tablet formulation) Pharmacokinetic Parameters in Patients with Advanced Solid Tumours

	C_{max} (µg/mL)[a]	t_{max} (h)[c]	$t_{½}$ (h)	$AUC_{0-\infty}$ (µg.h/mL)[a]	CL/F (L/h)[b]	Vd/F (L)[b]
Single 300 mg dose mean (SD or %GCV), n	7.3 (34), 102	1.5 (0.5 – 6), 102	15 (8.2), 100	47 (59), 100	~7.4 (3.9), 100	~158 (136), 100

[a] For C_{max} and AUC geometric mean (geometric percentage coefficient of variation) is shown.
[b] For $t_{1/2}$, CL/F and Vd/F arithmetic mean (standard deviation) is presented.
[c] For t_{max} median (range) is shown.

Absorption:

The absolute bioavailability of olaparib is unknown. Following a single oral administration of olaparib tablet formulation (2 x 150 mg), absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing.

Co-administration with food slowed the rate (t_{max} delayed by 2.5 hours and C_{max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC treatment ratio: 1.08; 90% CI: 1.01, 1.16). Consequently, patients should take LYNPARZA without regard to food (see DOSAGE AND ADMINISTRATION, Administration).

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 Tablet). 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:

The *in vitro* plasma protein binding is approximately 82% at 10 µg/mL which is approximately C_{max}.

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.

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 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.

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.

Elimination:

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.

Special Populations and Conditions

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

Age, Bodyweight or Ethnic origin: In population based PK analyses, patient age, gender, body weight or race (including Caucasian and Asian patients) were not significant covariates.

Hepatic Insufficiency: In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild hepatic impairment (based on Child-Pugh score) AUC increased by 15% and C_{max} by 13% compared with patients with normal hepatic function. No LYNPARZA dose adjustment is required in patients with mild hepatic impairment

(see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

LYNPARZA has not been studied in patients with moderate or severe hepatic impairment.

Renal Insufficiency: In a pharmacokinetic study, following a single oral 300 mg dose of olaparib (tablet formulation) to patients with mild renal impairment (creatinine clearance: 51 to 80 mL/min), AUC increased by 24% and C_{max} by 15% compared with patients with normal renal function. No LYNPARZA dose adjustment is required for patients with mild renal impairment.

Following a single oral 300 mg dose of LYNPARZA to patients with moderate renal impairment (creatinine clearance: 31 to 50 mL/min), AUC increased by 44% and C_{max} by 26% compared with patients with normal renal function. LYNPARZA dose reduction is recommended for patients with moderate renal impairment (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

LYNPARZA has not been studied in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤30 ml/min).

11 STORAGE, STABILITY AND DISPOSAL

Store LYNPARZA (olaparib) between 2 - 30°C in the original package in order to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

- *LYNPARZA (olaparib) indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA wild type high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy, has been issued **marketing authorization with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for LYNPARZA, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php.*

- *LYNPARZA has been issued **marketing authorization without conditions** as monotherapy for the:*
  - *Maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.*
  - *Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy. Germline BRCA mutation must be confirmed before LYNPARZA treatment is initiated.*

13 PHARMACEUTICAL INFORMATION

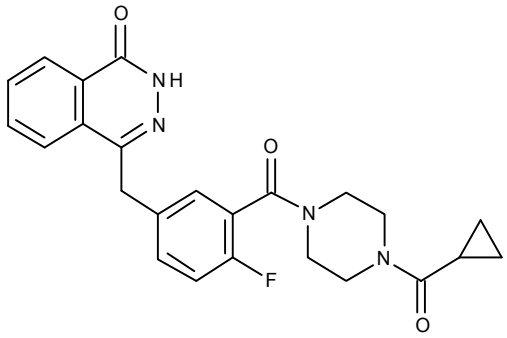
Drug Substance

Proper name/Common name: olaparib

Chemical name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one

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 199-206°C as measured by differential scanning calorimetry. The octanol/water (pH =7.4) partition coefficient: Log D =1.49. Olaparib is achiral.

14 CLINICAL TRIALS

14.1 Treatment of g*BRCA*m HER2-Negative Metastatic Breast Cancer (OlympiAD)

The safety and efficacy of LYNPARZA (olaparib) in the treatment of g*BRCA*m HER2-negative metastatic breast cancer was studied in a Phase III, randomized, open-label, multicentre, active-controlled trial, OlympiAD (Study D0819C00003). A total of 302 patients were randomized 2:1 to receive Lynparza 300 mg (2 x 150 mg tablets) twice daily or the active comparator (physician's choice of chemotherapy: capecitabine, eribulin, or vinorelbine, at standard doses [see Table 6]) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). The g*BRCA*m was confirmed using Myriad g*BRCA* test.

All patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the (neo)adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or had disease that the treating physician believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progression during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Patients could not have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease.

Trial Design and Study Demographics (OlympiAD)

Table 8 Summary of Trial Design for Clinical Trials in g*BRCA*m HER2-Negative Metastatic Breast Cancer Patients

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
D0819C00003 (OlympiAD)	Phase III randomized (2:1), open-label, active-controlled study, that investigated LYNPARZA 300 mg twice daily tablet formulation as treatment for patients with g*BRCA*m HER2-negative metastatic breast cancer	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=205 Physicians' choice of chemotherapy[a] n=97	LYNPARZA 45.0 years (22 – 76 years) Physicians' choice of chemotherapy[a] 45.9 years (24 – 68 years)	LYNPARZA Female: n=200 Male: n=5 Physicians' choice of chemotherapy[a] Female: n=95 Male: n=2

[a] Physician's choice of chemotherapy consisting of either capecitabine (2500 mg/m^2 oral daily, divided in 2 doses for 14 days, repeated every 21 days), eribulin (1.4 mg/m^2 IV Day 1 and Day 8, repeated every 21 days), or vinorelbine (30 mg/m^2 IV Day 1 and Day 8, repeated every 21 days).

Demographic and baseline patient characteristics were generally balanced between treatment groups in OlympiAD and are summarized below.

Table 9 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
Demographics		
Age (years)		
Mean (SD)	45.0 (10.9)	45.9 (10.3)
Median (range)	44.0 (22 – 76)	45.0 (24 – 68)
Age group (years), n (%)		
<50	138 (67.3)	63 (64.9)

Table 9 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
≥50 to <65	56 (27.3)	30 (30.9)
≥65	11 (5.4)	4 (4.1)
Sex, n (%)		
Female	200 (97.6)	95 (97.9)
Male	5 (2.4)	2 (2.1)
Race, n (%)		
Caucasian	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Black/African American	1 (0.5)	4 (4.1)
Other	4 (2.0)	2 (2.1)
Disease Characteristics		
ECOG performance status, n (%)		
Grade 0	148 (72.2)	62 (63.9)
Grade 1	57 (27.8)	35 (36.1)
Germline *BRCA* status		
BRCA1	114 (55.6)	50 (51.5)
BRCA2	84 (41.0)	45 (46.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Missing[b]	3 (1.5)	2 (2.1)
At the Time of Randomisation, was the Patient's Breast Cancer Progressing?		
Yes	159 (77.6)	73 (75.3)
De Novo Metastatic Disease[c]		
Yes	26 (12.7)	12 (12.4)
Prior Endocrine Therapy		
For metastatic disease	68 (33.2)	30 (30.9)
For localised disease (adjuvant and/or neoadjuvant)	80 (39.0)	36 (37.1)
Stratification Factors (IVRS Data)		
Received prior chemotherapy regimens for metastatic breast cancer[d], n (%)		
No	59 (28.8)	28 (28.9)
Yes	146 (71.2)	69 (71.1)

Table 9 Summary of Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set) in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid (n=205)	Physician's Choice of Chemotherapy[a] (n=97)
ER and PgR status[e], n (%)		
ER and/or PgR positive	103 (50.2)	49 (50.5)
ER and PgR negative	102 (49.8)	48 (49.5)
Prior use of platinum for breast cancer, n (%)[f]		
Yes	60 (29.3)	26 (26.8)

a Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
b Patients with Missing status were not confirmed as g*BRCA*m using the Myriad CDx g*BRCA* test. Within the LYNPARZA arm all 3 cases were determined as *BRCA1* by local or CLIA testing and within the physician's choice of chemotherapy arm 1 patient was *BRCA1* and 1 patient was *BRCA2*.
c Metastatic disease at time of initial diagnosis of breast cancer.
d According to the electronic case report form data, 68 patients in the LYNPARZA arm and 31 patients in the physician's choice of chemotherapy arm had not received prior chemotherapy regimens for metastatic breast cancer.
e According to the electronic case report form data, 102 patients in the LYNPARZA arm and 47 patients in the physician's choice of chemotherapy arm were ER and/or PgR positive. Patient E2806008 did not have PgR status assessed but was stratified to the ER negative and PgR negative subgroup for randomisation. The patient was excluded from summaries of eCRF data.
f According to the electronic case report form data, 55 patients in the LYNPARZA arm and 21 patients in the physician's choice of chemotherapy arm had prior use of platinum for breast cancer.

bid Twice daily; *BRCA* Breast cancer susceptibility gene; CDx Companion diagnostic; CLIA Clinical laboratory improvement amendments; ECOG Eastern cooperative oncology arm; eCRF electronic case report form; ER Estrogen receptor; FAS Full analysis set; g*BRCA* Germline *BRCA*; IVRS Interactive Voice Response System; PgR Progesterone receptor; SD Standard deviation.

Study Results (OlympiAD)

The primary endpoint in the OlympiAD study was progression-free survival (PFS) assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary endpoints included time to second progression or death (PFS2), overall survival (OS) and objective response rate (ORR). Response was assessed every 6 weeks for the first 24 weeks, and then every 12 weeks relative to date of randomization, until disease progression. A summary of key efficacy findings is presented in Table 10 and Figure 1.

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS for LYNPARZA compared with the comparator arm with a HR of 0.58 (95% CI 0.43-0.80; p=0.0009; median 7.0 months [95% CI 5.68-8.31] for LYNPARZA vs. 4.2 months [95% CI 2.79-4.27] for comparator). A sensitivity analysis using investigator-assessed PFS was consistent.

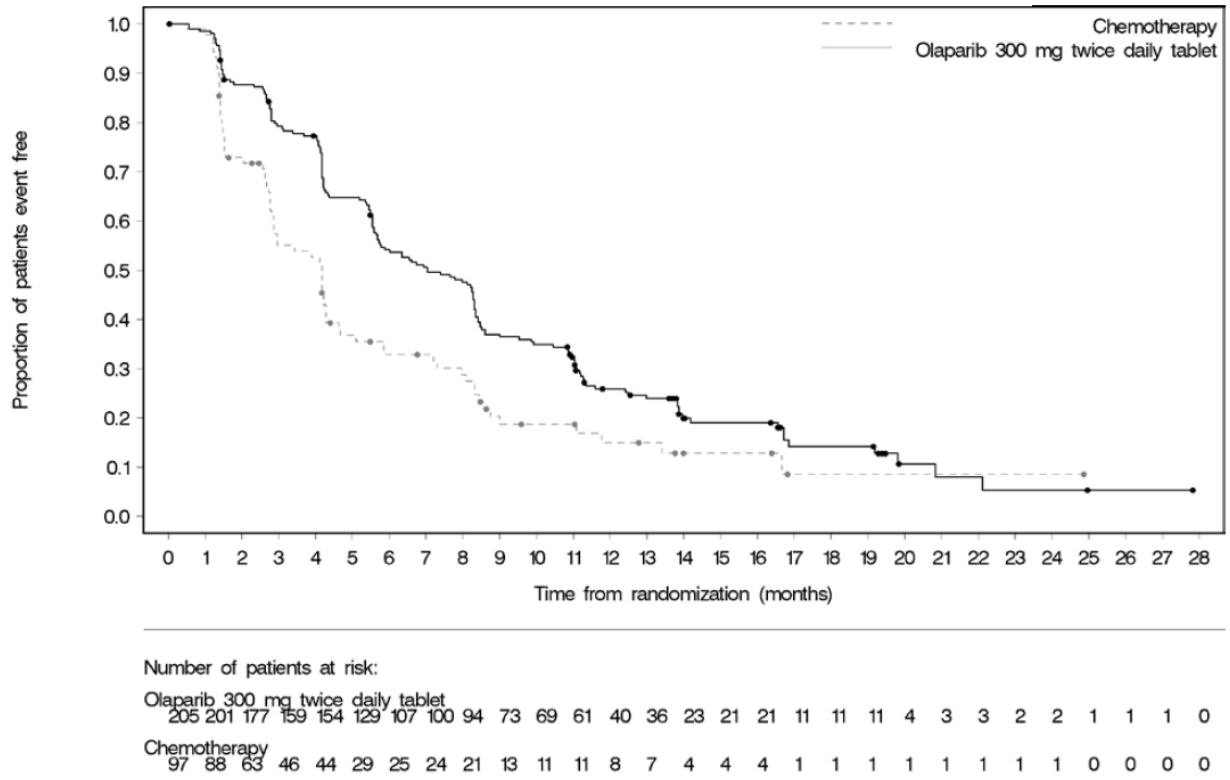
A statistically significant improvement in PFS2 was also observed with a HR of 0.57 (95% CI 0.40-0.83; p=0.0033; median 13.2 months for LYNPARZA vs 9.3 months for comparator). The median time to onset of response was 47 days for LYNPARZA vs 45 days for comparator. The median duration of response was 6.4 months (95% CI 5.0-7.2) for LYNPARZA vs 7.1 months (95% CI 3.2-12.2) for comparator. The OS data was 46% mature in the Full Analysis Set (FAS) at the time of analysis, with a median follow-up for censored patients of 16.2 months for LYNPARZA vs. 16.1 months for comparator (HR 0.90; 95% CI 0.63-1.29; p=0.5665; median 19.3 months for LYNPARZA vs 19.6 months for control).

Table 10 Summary of Key Efficacy Findings for Patients with g*BRCA*m HER2-Negative Metastatic Breast Cancer in the OlympiAD Study

	LYNPARZA Tablets 300 mg bid		Physician's Choice of Chemotherapy[a]
PFS (77% Maturity)			
Number of events: Total number of patients (%)	163:205 (80)		71:97 (73)
Median time (months)	7.0		4.2
Median time (95% CI)	5.7-8.3		2.8-4.3
HR (95% CI)		0.58 (0.43-0.80)	
P value (2-sided)		P=0.0009	
Interim OS (46% Maturity)			
Number of events: Total number of patients (%)	94:205 (46)		46:97 (47)[b]
Median time (months)	19.3		19.6
Median time (95% CI)	16.7-21.8		14.1-24.2
HR (95% CI)		0.9 (0.63-1.29)	
P value (2-sided)		P=0.5665	
ORR			
Number of objective responders: Total number of patients with measurable disease (%)[c]	100/167 (60)		19/66 (29)
95% CI	52.0 to 67.4		18.3 to 41.3

a Physician's choice of chemotherapy consisting of either capecitabine, eribulin or vinorelbine.
b Approximately a tenth of patients in the physician's choice group (8/97; 8.2%) received a subsequent PARP inhibitor.
c The complete response rate was 9% for LYNPARZA compared to 2% for chemotherapy arm.
N Number of events/number of randomised patients; bid Twice daily; CI Confidence interval; HR Hazard ratio; ORR Objective response rate; OS overall survival; PFS progression-free survival.

Figure 1 Progression Free Survival in Patients with g*BRCA*m HER2-Negative Metastatic Breast Cancer in the OlympiAD Study



14.2 Maintenance Treatment of Platinum-Sensitive Relapsed *BRCA-mutated* Ovarian Cancer (SOLO2)

The efficacy of LYNPARZA (olaparib tablets) in the maintenance treatment setting in platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer was investigated in a randomized phase III double-blind, placebo-controlled trial in patients with PSR, *BRCA*-mutated (*BRCA*m) disease (SOLO2). SOLO2 enrolled PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred more than 6 months after completion of penultimate platinum-based chemotherapy. 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. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad Clinical Laboratory Improvement Amendments (CLIA) Integrated BRAC*Analysis*® test, or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

Trial Design and Study Demographics (SOLO2)

Table 11 Trial Design for SOLO2 (Tablet Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D0816C00002 (SOLO2 Study)	Phase III randomized (2:1), double-blind, placebo-controlled study, that investigated olaparib 300 mg twice daily tablet formulation as a maintenance treatment for patients with *BRCA* mutated PSR ovarian cancer	300 mg (2 x 150 mg tablets) orally twice daily	LYNPARZA n=196 Placebo n=99	LYNPARZA = 57.0 years Placebo = 56.6 years	Female

Demographic and baseline patient characteristics in SOLO2 are summarized below.

Table 12 SOLO2 (Tablet Formulation): Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set)

	LYNPARZA 300 mg tablet bid (n=196)	Placebo (n=99)
Demographics		
Age (years)		
Mean (SD)	57.0 (9.2)	56.6 (8.9)
Median (range)	56.0 (28-83)	56.0 (39-78)
Age group (years), n (%)		
<50	38 (19.4)	25 (25.3)
≥50 to <65	118 (60.2)	52 (52.5)
≥65	40 (20.4)	22 (22.2)
Race, n (%)		
White	173 (88.3)	91 (91.9)
Black/African American	1 (0.5)	0
Asian	22 (11.2)	7 (7.1)
Other	0	1 (1.0)
Ethnic group, n (%)		
Hispanic or Latino	10 (5.1)	1 (1.0)
Disease Characteristics		
ECOG Performance status, n (%)		
(0) Normal activity	162 (82.7)	77 (77.8)
(1) Restricted activity	32 (16.3)	22 (22.2)
(2) In bed <50% of the time	0	0
Unknown	2 (1.0)	0
Histology type, n (%)		
Serous	183 (93.4)	86 (86.9)
Endometrioid	9 (4.6)	8 (8.1)

Table 12 SOLO2 (Tablet Formulation): Selected Demographic and Patient Characteristics at Baseline (Full Analysis Set)

	LYNPARZA 300 mg tablet bid (n=196)	Placebo (n=99)
Mixed, Epithelial	3 (1.5)	4 (4.0)
Other	0	1 (1.0)
Serous, pappilliferum, endometrioid	0	1 (1.0)
Missing	1 (0.5)	0
Tumour Characteristics		
Primary tumour location, n (%)		
Ovary	162 (82.7)	86 (86.9)
Fallopian tube	13 (6.6)	4 (4.0)
Primary peritoneal	18 (9.2)	9 (9.1)
Other	2 (1.0)	0
Missing	1 (0.5)	0
Previous Treatments		
Response to previous platinum chemotherapy (recorded at randomization by IVRS), n (%)[a]		
PR	105 (53.6)	52 (52.5)
CR	91 (46.4)	47 (47.5)
Time to disease progression in the penultimate platinum-based chemotherapy prior to enrolment (recorded at randomization by IVRS), n (%)[b]		
>6 to ≤12 months	79 (40.3)	40 (40.4)
>12 months	117 (59.7)	59 (59.6)
Number of prior chemotherapies, n (%)		
2	108 (55.1)	60 (60.6)
3	54 (27.6)	21 (21.2)
4 or more	33 (16.8)	18 (18.2)
Median (range)	2.0 (2-7)	2.0 (2-13)
Number of prior platinum-containing chemotherapies, n (%)		
2	110 (56.1)	62 (62.6)
3	60 (30.6)	20 (20.2)
4 or more	25 (12.8)	17 (17.2)
Median (range)	2.0 (2-7)	2.0 (2-7)

a Objective Response: CR = Patients with no target lesions and no non-target lesions are baseline; PR = Patients with target lesions and/or non-target lesions at baseline. Note: This is the response from the platinum regimen just prior to therapy.

b Platinum sensitivity = time to progression after the completion of platinum chemotherapy. Note: Platinum sensitivity refers to the penultimate platinum not the platinum regimen that was just completed by the patient.

bid Twice daily; CR Complete response; CSR Clinical study report; ECOG Eastern Cooperative Oncology Group; FAS Full analysis set; IVRS Interactive voice response system; PR Partial response; SD Standard deviation

SOLO2 Results

The study compared the efficacy of LYNPARZA (olaparib) maintenance treatment [300 mg (2 x 150 mg tablets) twice daily] taken to progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomization: 196 LYNPARZA and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy. All patients had evidence of germline *BRCA* mutation (g*BRCA*m) at baseline.

The primary endpoint was progression-free survival (PFS) determined by investigator assessment using RECIST 1.1. A secondary efficacy endpoint was overall survival (OS). A summary of key efficacy findings is presented in Table 13 and Figure 2.

The study met its primary objective demonstrating a clinically meaningful and statistically significant improvement in investigator assessed PFS for LYNPARZA compared with placebo with a HR of 0.30. The investigator assessment of PFS was supported with a blinded independent central radiological review of PFS (HR 0.25; 95% CI 0.18-0.35; p<0.0001; median 30.2 months for LYNPARZA vs. 5.5 months for placebo). At 2 years, 43% LYNPARZA-treated patients remained progression-free compared with only 15% placebo-treated patients. Interim OS was immature with events in only 24% of patients.

Table 13 Key Efficacy Findings for Patients with g*BRCA*mutated PSR Ovarian Cancer in SOLO2

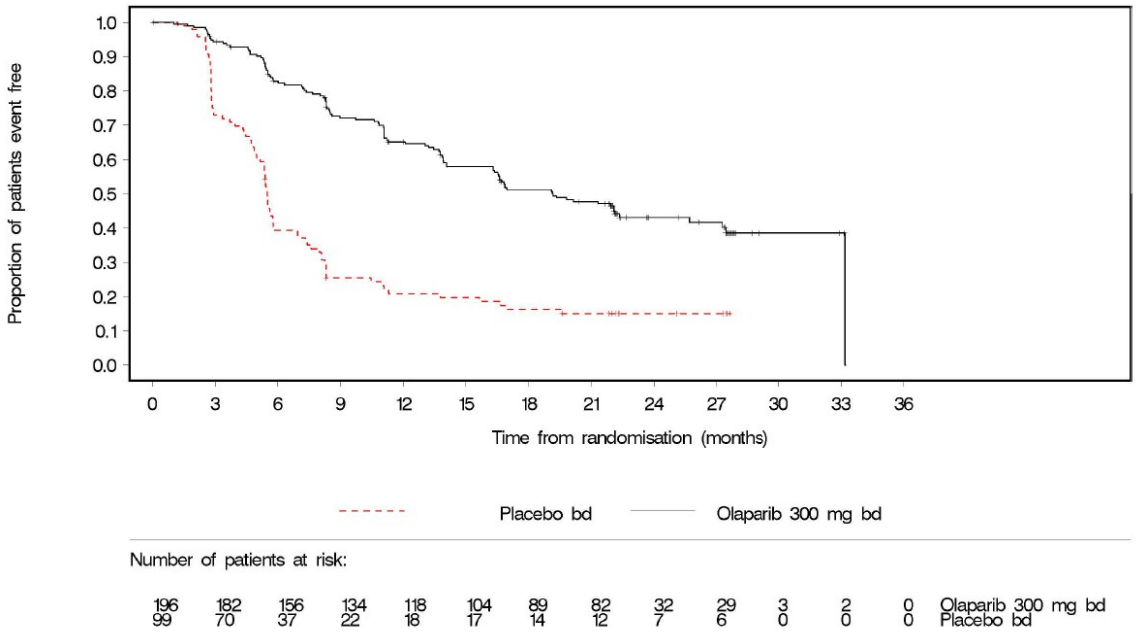
	LYNPARZA 300 mg tablet bid	Placebo
PFS (63% maturity)		
Number of events:Total number of patients (%)	107:196 (55)	80:99 (81)
Median time (months)	19.1	5.5
HR (95% CI)[a]	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	
Interim OS (24% maturity)		
Number of events: Total number of patients (%)	45:196 (23)	27:99 (27)[b]
Median time (months)	NR	NR
HR (95% CI)[a]	0.80 (0.50-1.31)	
P value (2-sided)	p=0.4267	

[a] HR= Hazard Ratio. A value <1 favours LYNPARZA. The analysis was performed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy.

[b] Approximately a third of placebo-treated patients (28/99; 28.3%) received a subsequent PARP inhibitor.

bid Twice daily; NR not reached; OS overall survival; PFS progression-free survival; CI confidence interval

Figure 2 SOLO2: Kaplan-Meier Plot of PFS in Patients with g*BRCA*mutated PSR Ovarian Cancer[a]



[a] 63% Maturity - Investigator Assessment

The secondary endpoints included time from randomization to second progression or death ([PFS2], HR of 0.50, 95% CI 0.34-0.72, p=0.0002, median not reached for LYNPARZA vs 18.4 months placebo) and time from randomization to start of first subsequent therapy or death ([TFST], HR of 0.28, 95% CI 0.21-0.38, nominal p<0.0001, median 27.9 months LYNPARZA vs 7.1 months placebo).

Treatment with LYNPARZA did not negatively impact patient reported outcomes or health related quality of life as assessed by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

The use of LYNPARZA in the maintenance treatment setting for *BRCA*m patient population is supported by data from a randomized, phase II, double-blind, placebo-controlled trial (Study 19) (see Section 14.3).

NOC/c

14.3 Maintenance Treatment of Platinum-Sensitive Relapsed *BRCA* wild type Ovarian Cancer (Study 19)

The efficacy of LYNPARZA (olaparib capsules) in the maintenance treatment setting in PSR *BRCA*-mutated and *BRCA* wild type ovarian, fallopian tube or primary peritoneal cancer was investigated in a randomized phase II double-blind, placebo-controlled trial in patients with PSR disease (Study 19). Study 19 enrolled PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred more than 6 months after completion of penultimate platinum-based chemotherapy. 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. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad Clinical Laboratory Improvement Amendments (CLIA) Integrated BRAC*Analysis*® test, or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

Trial Design and Study Demographics (Study 19)

Table 14 Trial Design for Study 19 (Capsule Formulation)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D0810C00019 (Study 19)	Phase II, randomized, double-blind, placebo-controlled maintenance study of olaparib compared to placebo in PSR high grade serous ovarian cancer patients	400 mg (8 x 50 mg capsules formulation) orally twice daily	**All patients:** LYNPARZA n=136 Placebo n=129 ***BRCA*-mutated patients:** LYNPARZA n=74 Placebo n=62 ***BRCA* wild type patients:** LYNPARZA n=57 Placebo n=61	LYNPARZA = 58.9 years Placebo = 58.5 years	Female

Demographic and baseline patient characteristics were generally well balanced between treatment groups for all patients in Study 19 and are summarized below.

Table 15 Study 19 (Capsule Formulation): Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set)

	All Patients		***BRCA*-mutated**		***BRCA* wild type**	
	LYNPARZA 400 mg capsule bid n=136	**Placebo n=129**	**LYNPARZA 400 mg capsule bid n=74**	**Placebo n=62**	**LYNPARZA 400 mg capsule bid n=57**	**Placebo n=61**
Demographics						
Age (years)						
Mean (standard deviation)	58.9 (10.95)	58.5 (9.89)	57.6 (10.37)	55.5 (10.53)	60.8 (11.69)	62.1 (7.82)
Median (range)	58.0 (21 to 89)	59.0 (33 to 84)	57.5 (38 to 89)	55.0 (33 to 84)	62.0 (21-80)	63.0 (49-79)
Age group, n (%)						
<50 years	30 (22.1)	20 (15.5)	19 (25.7)	16 (25.8)	10 (17.5)	1 (1.6)

Table 15 Study 19 (Capsule Formulation): Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA 400 mg capsule bid n=136	Placebo n=129	LYNPARZA 400 mg capsule bid n=74	Placebo n=62	LYNPARZA 400 mg capsule bid n=57	Placebo n=61
≥50 to <65 years	61 (44.9)	74 (57.4)	38 (51.4)	35 (56.5)	20 (35.1)	37 (60.7)
≥65 years	45 (33.1)	35 (27.1)	17 (23.0)	11 (17.7)	27 (47.4)	23 (37.7)
Race, n (%)						
White	130 (95.6)	126 (97.7)	70 (94.6)	61 (98.4)	55 (96.5)	59 (96.7)
Black or African American	2 (1.5)	1 (0.8)	2 (2.7)	0	0	1 (1.6)
Asian	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Other	2 (1.5)	0	1 (1.4)	0	1 (1.8)	0
Disease Characteristics						
ECOG PS, n (%)						
(0) Normal activity	110 (80.9)	95 (73.6)	62 (83.8)	45 (72.6)	45 (78.9)	45 (73.8)
(1) Restricted activity	23 (16.9)	30 (23.3)	11 (14.9)	15 (24.2)	10 (17.5)	14 (23.0)
(2) In bed ≤50% of the time	1 (0.7)	2 (1.6)	0	1 (1.6)	1 (1.8)	1 (1.6)
Unknown	2 (1.5)	2 (1.6)	1 (1.4)	1 (1.6)	1 (1.8)	1 (1.6)
Tumour Characteristics						
Primary tumour location						
Ovary	119 (87.5)	109 (84.5)	65 (87.8)	54 (87.1)	50 (87.7)	49 (80.3)
Fallopian tube	3 (2.2)	3 (2.3)	1 (1.4)	2 (3.2)	2 (3.5)	1 (1.6)
Primary peritoneal	14 (10.3)	16 (12.4)	8 (10.8)	6 (9.7)	5 (8.8)	10 (16.4)
Other	0	1 (0.8)[a]	0	0	0	1 (1.6)
Tumour grade						
Well differentiated (G1)	0	0	0	0	0	0

Table 15 Study 19 (Capsule Formulation): Selected Demographic and Patient Characteristics at Baseline for the Overall Population and Subgroups Based on *BRCA* Status (Full Analysis Set)

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA 400 mg capsule bid n=136	Placebo n=129	LYNPARZA 400 mg capsule bid n=74	Placebo n=62	LYNPARZA 400 mg capsule bid n=57	Placebo n=61
Moderately differentiated (G2)	36 (26.5)	34 (26.4)	17 (23.0)	15 (24.2)	15 (26.3)	16 (26.2)
Poorly differentiated (G3)	97 (71.3)	89 (69.0)	55 (74.3)	46 (74.2)	41 (71.9)	41 (67.2)
Undifferentiated (G4)	2 (1.5)	4 (3.1)	1 (1.4)	0	1 (1.8)	4 (6.6)
Unassessable (GX)	1 (0.7)	2 (1.6)	1 (1.4)	1 (1.6)	0	0
Number of previous chemotherapy regimens						
Mean	3.1	2.9	3.3	3.0	2.8	2.7
Median (range)	3 (2-11)	3 (2-8)	3 (2-11)	3 (2-8)	2 (2-8)	2 (2-8)
Number of previous platinum-containing chemotherapies						
Mean	2.6	2.5	2.8	2.5	2.5	2.4
Median (range)	2 (2-7)	2 (2-8)	2 (2-7)	2 (2-6)	2 (2-5)	2 (1-5)

*BRCA*m = Breast cancer susceptibility gene-mutated; ECOG PS = Eastern Cooperative Oncology Group performance status; n = Total number of patients.
*BRCA*m subgroup included patients with germline and/or somatic *BRCA* mutation.

Study 19 Results

The study compared the efficacy of LYNPARZA (olaparib capsule) maintenance treatment [400 mg (8 x 50 mg capsules) twice daily] taken to progression with placebo treatment in 265 (136 LYNPARZA and 129 placebo) PSR patients who were in response (CR [complete response] or PR [partial response]) following completion of platinum-containing chemotherapy. The primary endpoint was progression-free survival (PFS) based on investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Secondary efficacy endpoints included overall survival (OS) and disease control rate (DCR).

A summary of key efficacy findings for all patients regardless of *BRCA* status and patients with *BRCA*m and *BRCA* wild type PSR ovarian cancer in Study 19 is presented in Table 16, Figure 3 and Figure 4. The study met its primary objective demonstrating a statistically significant and clinically relevant improvement in PFS for LYNPARZA compared with placebo with a hazard ratio (HR) of 0.35. At the final OS analysis at 79% maturity, the HR comparing LYNPARZA with placebo was 0.73.

In the LYNPARZA-treated group, 23.5% of patients remained on treatment for ≥2 years and 13.2% for ≥5 years. In the placebo-treated group, 3.9% of patients remained on treatment for ≥2 years and 0.8% for ≥5 years. TFST and TSST were also longer for LYNPARZA-treated patients.

Table 16 Key Efficacy Findings for the Overall Population and Subgroups Based on *BRCA* Status in Study 19

	All Patients		*BRCA*-mutated		*BRCA* wild type	
	LYNPARZA 400 mg capsule bid	**Placebo**	**LYNPARZA 400 mg capsule bid**	**Placebo**	**LYNPARZA 400 mg capsule bid**	**Placebo**
PFS						
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)	32:57 (56)	44:61 (72)
Median time (months)	8.4	4.8	11.2	4.3	7.4	5.5
HR (95% CI)[a]	0.35 (0.25-0.49)		0.18 (0.10–0.31)		0.54 (0.34-0.85)	
P value (2-sided)	p<0.00001		p<0.00001		p=0.00745	
OS						
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]	45:57 (79)	57:61 (93)
Median time (months)	29.8	27.8	34.9	30.2	24.5	26.6
HR (95% CI)[a]	0.73 (0.55–0.95)		0.62 (0.42–0.93)		0.84 (0.57-1.25)	
P value[*] (2-sided)	p=0.02138		p=0.02140		p=0.39749	

[*] There was no strategy for multiple testing in place for the sub-group analyses, thus all p values are nominal.

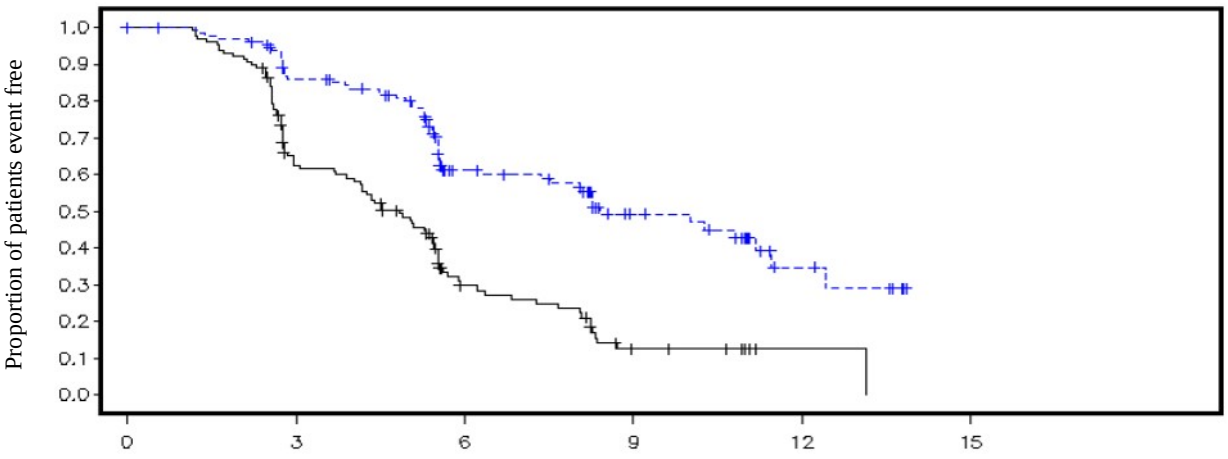
[a] HR= Hazard Ratio. A value <1 favours LYNPARZA. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.

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

N Number of events/number of randomized patients; bid Twice daily; OS overall survival; PFS progression-free survival; DCO data cut off; CI confidence interval.

DCO (PFS 30 June 2010; OS 09 May 2016)

Figure 3 Study 19: Kaplan-Meier Plot of PFS in the Full Analysis Set[a]



Time from randomization (months)

----------Placebo bid - - - - - - - - - LYNPARZA 400 mg bid

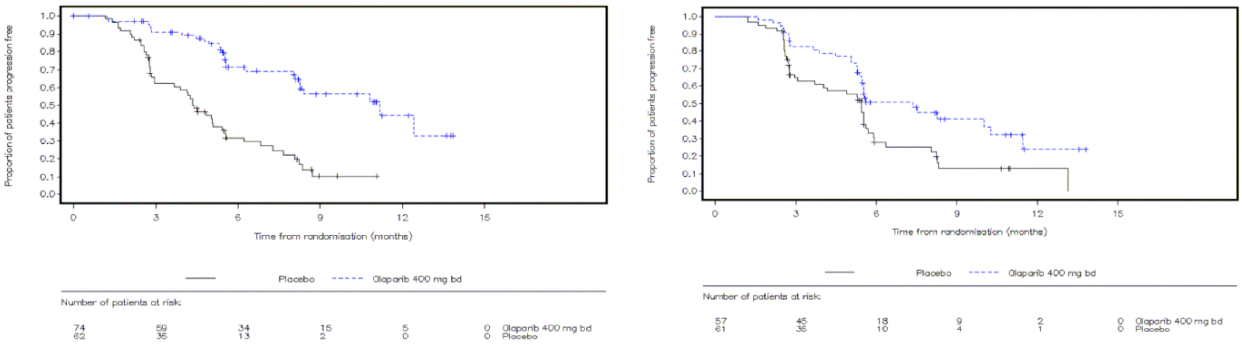
Number of patients at risk:

136	106	53	24	7	0	LYNPARZA 400 mg bid
129	72	24	7	1	0	Placebo

[a] (58% Maturity - Investigator Assessment) DCO 30 June 2010

Figure 4 Study 19: Kaplan-Meier Plot of PFS in the Full Analysis Set (*BRCA*-mutated and *BRCA* wild type)[a]

***BRCA*-mutated** ***BRCA* wild type**



[a] (58% Maturity - Investigator Assessment) DCO 30 June 2010

Within the overall population, the DCR at 24 weeks was 53% and 25% for patients in the LYNPARZA and placebo groups, respectively.

14.4 Comparative Bioavailability Studies

Based on a within patient comparison of capsule and tablet formulation, exposure to olaparib (AUC) following 300 mg single dose was 31% higher than that observed following 400mg capsule single dose (n=6).

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL 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 7- to 27-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 euthanized prematurely on Day 5. The mean total exposure to olaparib in these dogs was approximately 3- to 8-fold below that achieved in humans at the clinical dose of 300 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 5- to 11-fold below those seen at the clinical dose (300 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 300 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 the same as the clinical exposure at 300 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 5- to 11-fold below those achieved in humans at the clinical dose of 300 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 exposure at the highest dose in this study was approximately 14-fold lower than that achieved in humans at the recommended therapeutic dose of 300 mg twice daily.

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 63-fold lower than the mean clinical exposure at the recommended 300 mg twice daily 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 360-fold lower than that achieved at the clinical dose of 300 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 plasma concentration at the 0.05 mg/kg/day was about 450-fold lower than those seen in humans at the clinical dose of 300 mg bid.

Overall, since exposures in rats were substantially lower than those achieved in humans at the

300 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.

17 SUPPORTING PRODUCT MONOGRAPHS

LYNPARZA is also available as a 50 mg capsule. The tablets and capsules are not to be used interchangeably due to differences in the dosing of each formulation.

Refer to the LYNPARZA® 50 mg capsules Product Monograph (AstraZeneca Canada Inc.) for more details.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr LYNPARZA®

Olaparib Tablets

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**.

What are LYNPARZA tablets used for?

LYNPARZA is used to treat a type of breast cancer that has spread outside the breast in adults who have inherited changes (mutations) in the *BRCA* genes. *BRCA* genes are known as the breast cancer genes. A test is used to determine if there is a mutation in your breast cancer genes. To receive LYNPARZA for your breast cancer, you must have this mutation and have had previous chemotherapy for your breast cancer. You may also have had hormone therapy for your breast cancer.

- In patients with breast cancer, LYNPARZA has been approved ***without conditions***. This means it has passed Health Canada's review and can be bought and sold in Canada.

LYNPARZA is for adults with cancer of the ovaries. It is also for some other closely related cancers. When the cancer responds to chemotherapy, LYNPARZA helps to keep that response.

- In patients without *BRCA mutation*
  LYNPARZA has been approved ***with conditions*** **(NOC/c)**. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.
- In patients with *BRCA mutation*
  LYNPARZA has been approved ***without conditions***. This means it has passed Health Canada's review and can be bought and sold in Canada.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively

monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

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 a 50 mg capsule. The doses of LYNPARZA tablets and capsules are not the same. Taking the wrong dose or a capsule instead of a tablet could lead to LYNPARZA not working properly or to more side effects. Do not take more than 4 tablets per day.
- LYNPARZA can harm your unborn baby if you take it while you are pregnant.

How does LYNPARZA work?
LYNPARZA is a type of drug called a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor. PARP inhibitors can destroy cancer cells that are not able to repair damage to their DNA (genes).

Some people with ovarian cancer or breast cancer have mutations in genes called *BRCA* (known as the breast cancer gene). For ovarian cancer, LYNPARZA works in people with and without these mutations, however it works best in people who have them. For breast cancer, LYNPARZA works in people with these mutations. A test is used to determine whether you have a mutation of your *BRCA* genes.

What are the ingredients in LYNPARZA tablets?
Medicinal ingredients: olaparib
Non-medicinal ingredients: Colloidal silicon dioxide, Copovidone, Hypromellose, Iron oxide black (150 mg tablet only), Iron oxide yellow, Macrogol 400, Mannitol, Sodium stearyl fumarate, Titanium dioxide.

LYNPARZA comes in the following dosage forms:
Tablets: 100 mg and 150 mg

PLEASE NOTE: LYNPARZA is also available as a 50 mg **capsule**.

Risk of Medication Error: The doses of LYNPARZA tablets and capsules are not the same. Taking the wrong dose or a capsule instead of a tablet could lead to LYNPARZA not working properly or to more side effects. Do NOT take more than 4 tablets per day.

Do not use LYNPARZA if:
- You are allergic to olaparib or any of the other ingredients in 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 or liver disease.

Other warnings you should know about:
Female Patients:
- 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 1 month after taking your last dose of LYNPARZA. If you are planning to breast-feed, tell your doctor.

Male Patients:
- Use a condom when having sexual intercourse with a woman (even if she is pregnant). The condom must be used:
  - while you are taking LYNPARZA, and
  - for 3 months after you take your last dose of LYNPARZA.
- Your female partner must also use an effective method of birth control.
- Do not donate sperm while taking LYNPARZA and for 3 months after stopping LYNPARZA.

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.
- 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.

- 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.
- Modafinil - used to treat a sleep disorder called narcolepsy.
- 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, Seville oranges or similar fruits while taking LYNPARZA. They can affect the way the medicine works.

How to take LYNPARZA tablets:
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 TABLETS for you.
- Swallow whole. Do NOT chew, crush, dissolve or divide the tablets. This may affect how quickly the drug gets into your body.
- Take at about the same time each morning and evening.
- Take with or without food.
- Never take more than 4 tablets in a day.
- For ovarian cancer: Start taking LYNPARZA within 8 weeks of your last dose of platinum-containing chemotherapy.

Recommended Total Daily Dose for Tablets:
Adult Daily Dose 600 mg: take two 150 mg tablets twice a day.
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.

Reduced Total Daily Doses for Tablets:
Adult Daily Dose 500 mg: take one 150 mg tablet and one 100 mg tablet twice a day.
Adult Daily Dose 400 mg: take two 100 mg tablets twice a day.
Adult Daily Dose 300 mg: take one 150 mg tablet twice a day.
Adult Daily Dose 200 mg: take one 100 mg tablet 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 forgotten tablets.

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
- Fever

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, or weakness.		X	
Nausea and Vomiting: Feeling sick. Being sick or throwing up.	X		
COMMON			
Neutropenia or Leukopenia (low white blood cells: neutrophils and leukocytes): Fever or infection, fatigue, aches and pains, and flu-like symptoms.		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	
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
Cystitis (inflammation of the bladder): Urge to urinate more often, uncomfortable or painful urination, cloudy, dark or strong smelling urine, blood in urine.	X		
Thrombocytopenia (low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness.		X	
UNCOMMON			
Lymphopenia (low white blood cells: lymphocytes): Get infections more easily.		X	
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 between 2 - 30°C.
- Store in the original package in order to protect from moisture.
- 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
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.astrazeneca.ca), or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to date version can be found at www.astrazeneca.ca.

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

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