PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

Breast Cancer

1 LYNPARZA (olaparib) is indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Patients must have confirmation of a germline *BRCA* mutation before LYNPARZA treatment is initiated.

2 • Marketing authorization with conditions issued based on invasive disease-free survival (iDFS) and distant disease-free survival (DDFS) (see 14 CLINICAL TRIALS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in subsequent analyses.

3 LYNPARZA is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m), 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

4 LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy. Patients must have confirmation of *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

5 • Marketing authorization without conditions issued for ovarian cancer patients with *BRCA* mutation who are in response to first-line platinum-based chemotherapy was based on results from a randomized, placebo-controlled phase III trial (SOLO1) demonstrating that olaparib tablet is superior to placebo in prolonging progression-free survival (PFS) in patients with *BRCA* mutation, as assessed by investigator using RECIST 1.1 (see 14 CLINICAL TRIALS).

6 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.

7 • Marketing authorization with conditions issued for ovarian cancer patients with *BRCA* wild type status was based on promising evidence of superior benefit in prolonging 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 14 CLINICAL TRIALS, Comparative Bioavailability Studies.

8 • Marketing authorization without conditions issued for PSR 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 1.1 (see 14 CLINICAL TRIALS).

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

2 Adenocarcinoma of the Pancreas
LYNPARZA is indicated as monotherapy for the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) metastatic adenocarcinoma of the pancreas whose disease has not progressed on a minimum of 16 weeks of first-line platinum-based chemotherapy. Germline *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated.

3 Prostate Cancer
LYNPARZA is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA* or *ATM* mutated metastatic castration-resistant Prostate Cancer (mCRPC) who have progressed following prior treatment with a new hormonal agent. *BRCA* or *ATM* mutations must be confirmed before LYNPARZA treatment is initiated.

1.1 Pediatrics

4 **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

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

2 CONTRAINDICATIONS

6 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

7

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 7 Carcinogenesis and Mutagenesis and 8.1 Myelodysplastic syndrome/Acute myeloid leukemia).
- Pneumonitis has been reported in a small number of patients receiving LYNPARZA, and

some reports have been fatal. (See 7 Respiratory).

- LYNPARZA could cause fetal harm when administered to a pregnant woman (see 7 Reproductive Health Female and Male Potential).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

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, see 7 Hematologic).

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Grapefruit, star fruit, pomegranate and Seville oranges or their juices which are known to inhibit CYP3A should not be consumed while taking LYNPARZA (see 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

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 adjuvant treatment of g*BRCA*m HER2-negative high risk early breast cancer: It is recommended that patients are treated for a total of 1 year, or until disease recurrence or unacceptable toxicity, whichever occurs first. Patients with hormone receptor positive breast cancer should continue concurrent treatment with endocrine therapy as per current clinical practice guidelines.

For treatment of metastatic HER2-negative *gBRCAm* breast cancer: It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity.

For maintenance treatment of patients with *BRCAm* advanced ovarian cancer who are in response to first-line platinum-based chemotherapy:
Patients can continue treatment for 2 years or until disease progression.

Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment.

Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

For maintenance treatment of PSR 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 8 ADVERSE REACTIONS). It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity.

For maintenance treatment of patients with *gBRCAm* metastatic adenocarcinoma of the pancreas who are in response to first-line platinum-based chemotherapy: It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

For treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and mutations in the *BRCA* and *ATM genes*:
It is recommended that LYNPARZA treatment be continued until progression of the underlying disease or unacceptable toxicity. Patients receiving LYNPARZA for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently, or should have had bilateral orchiectomy.

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 8 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 7 WARNINGS AND PRECAUTIONS and 9 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 pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 - 80 ml/min) with no dose adjustment (see 10.3 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 10.3 Pharmacokinetics).

1 Hepatic Insufficiency: LYNPARZA (olaparib tablets) can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see 10.3 Pharmacokinetics). LYNPARZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients.

4.4 Administration

2 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.

4.5 Missed Dose

3 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

4 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

5 **Table 1 Dosage Forms, Strengths, Composition and Packaging**

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Use	Tablet 100 mg, 150 mg	Colloidal silicon dioxide, copovidone, hypromellose, iron oxide black (150 mg tablet only), iron oxide yellow, macrogol 400, mannitol, sodium stearyl fumarate, titanium dioxide.

Dosage Form Description

LYNPARZA (olaparib) 150 mg tablet is a green to green/grey film-coated, 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 film-coated, 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.

9

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

1 Interactions with other medicinal products

Co-administration of LYNPARZA (olaparib) with strong or moderate CYP3A inhibitors is not recommended (see 9 DRUG INTERACTIONS). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see 4.2 Recommended Dose and Dosage Adjustment).

2 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 9 DRUG INTERACTIONS).

3 **Carcinogenesis and Mutagenesis**

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was reported with an incidence of approximately 1% in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow up. In a Phase III clinical trial (SOLO2), a substantially higher incidence was reported in patients with *BRCAm* platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see 8.1 Myelodysplastic syndrome/Acute myeloid leukemia). The majority of events had a fatal outcome. The duration of therapy with LYNPARZA in patients who developed MDS/AML varied from < 6 months to > 4 years. 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.

Cardiovascular

4 Venous Thromboembolic Events

Venous thromboembolic events (VTE), including pulmonary embolism, have occurred in patients treated with LYNPARZA and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer who, also received androgen deprivation therapy, compared with other approved indications. Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

5 **Driving and Operating Machinery**

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

6 **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, 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. Patients

1 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.

2 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
Genetic Testing

3 *BRCA* and *ATM* mutation status should be determined by an experienced laboratory using a validated test method.

4 *For adjuvant treatment of gBRCAm HER2-negative high risk early breast cancer*: Patients must have confirmation of a deleterious or suspected deleterious germline *BRCA* mutation before LYNPARZA treatment is initiated.

5 *For treatment of metastatic HER2-negative gBRCAm breast cancer:* Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

6 *For maintenance treatment of patients with BRCAm advanced ovarian cancer who are in response to first-line platinum-based chemotherapy:* Patients must have confirmation of *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

7 *For maintenance treatment of patients with gBRCAm metastatic adenocarcinoma of the pancreas who are in response to first-line platinum-based chemotherapy:* Patients must have confirmation of a deleterious or suspected deleterious *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

8 *For treatment of BRCA or ATM-gene mutated metastatic castration-resistant prostate cancer (mCRPC):*
Patients must have confirmation of a deleterious or suspected deleterious germline and/or somatic *BRCA* or *ATM* gene mutation before LYNPARZA treatment is initiated.

9 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 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

10 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 (See 7 Hematologic).

1 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 for 6 months after receiving the last dose of LYNPARZA (see 7.1 Special Populations).

Reproductive Health Female and Male Potential

2 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 7.1 Special Populations and 16 NON-CLINICAL TOXICOLOGY).

3 Women of childbearing potential must use two forms of reliable contraception before starting LYNPARZA treatment, during therapy and for 6 months after receiving the last dose of LYNPARZA.

4 Since it cannot be excluded that LYNPARZA may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with LYNPARZA. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see 9.4 Drug-Drug Interactions). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

5 Male patients should be advised that they must use effective contraception during LYNPARZA treatment 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. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA (see 7.1.1 Pregnant Women).

6 **Respiratory**
Pneumonitis (grade 3 or higher) has been reported in 0.9% 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.

7.1 Special Populations

7.1.1 Pregnant Women

7 There are no clinical data regarding the use of LYNPARZA in pregnant women or the impact on fertility. LYNPARZA should not be used during pregnancy due to the potential teratogenic, genotoxic and embryofetal effects (see 16 NON-CLINICAL TOXICOLOGY). Female partners of male patients taking LYNPARZA should also avoid pregnancy.

1 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.

2 Contraception and pregnancy testing
Women of childbearing potential must use two forms of reliable contraception before starting LYNPARZA treatment, during therapy and for 6 months after receiving the last dose of LYNPARZA. Two highly effective and complementary forms of contraception are recommended. 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 for 6 months after receiving the last dose of LYNPARZA.

3 Since it cannot be excluded that LYNPARZA may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with LYNPARZA. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see 9.4 Drug-Drug Interactions). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

4 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

5 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

6 **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

7 **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

8 LYNPARZA (olaparib tablets) can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment. LYNPARZA is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

7.1.6 Renal insufficiency

9 For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the

1 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 pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 - 80 ml/min) with no dose adjustment (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

2 The safety of LYNPARZA (olaparib) was evaluated in a pooled safety dataset of 4098 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 (See Table 2).

3 The most commonly reported adverse reactions (in ≥20% of patients) from LYNPARZA monotherapy pooled studies (n=4098) were nausea, fatigue (including asthenia), anemia, vomiting, diarrhea and decreased appetite. These reactions were generally CTCAE grade 1 or 2, intermittent in nature and managed by standard supportive treatments or LYNPARZA dose modification. The most commonly reported adverse reactions (in ≥1% of patients) with CTCAE grade ≥3 severity were anemia, neutropenia, fatigue (including asthenia), leukopenia, thrombocytopenia, lymphopenia, vomiting, nausea, diarrhea and dyspnea.

4 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.

5 The most commonly reported serious adverse event (SAE) (in ≥1% of patients) was anemia (4.1%).

6 The overall frequency of adverse events leading to discontinuation of LYNPARZA was 5.9%.The frequencies of adverse reactions (in >0.2% of patients) leading to discontinuation of LYNPARZA treatment were anemia (1.7%), nausea (1.0%), fatigue (including asthenia) (0.9%), thrombocytopenia (0.7%), neutropenia (0.6%), vomiting (0.5 %), leukopenia (0.3%) and MDS/AML (0.3%).

7 The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organized by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 2. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000) including isolated reports.

Table 2 Adverse Drug Reactions reported in Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Blood and lymphatic system disorders	Anemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Common	Common
	Lymphopenia[a]	Common	Common
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/Acute myeloid leukemia[a]	Uncommon	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia[a]	Very common	-
Respiratory, thoracic and mediastinal disorders	Dyspnea[a]	Very common	Common
	Cough[a]	Very common	Uncommon
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhea	Very common	UnCommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis[a]	Common	Uncommon
	Upper abdominal pain	Common	Rare
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	Rare
	Erythema nodosum	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Rare

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Mean cell volume increased	Uncommon	-
Vascular disorders	Thromboembolism (venous)	Common	Common

a Anemia includes preferred terms (PTs) of anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia and red blood cell count decreased.
Cough includes PTs of cough and productive cough.
Dermatitis includes PTs of dermatitis and dermatitis allergic.
Dysgeusia includes PTs of dysgeusia and taste disorder.
Dyspnea includes PTs of dyspnea and dyspnea exertional.
Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.
Leukopenia includes PTs of leukopenia and white blood cell count decreased.
Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia
MDS/AML includes PTs of acute myeloid leukemia, myelodysplastic syndrome and myeloid leukemia.
Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased.
Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.
Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia.
Thromboembolism (venous) includes PTs of embolism, pulmonary embolism, thrombosis, deep vein thrombosis and venous thrombosis.
Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

MedDRA version 24; CTCAE Common Terminology Criteria for Adverse Events

Hematological toxicity

Anemia was the most common CTCAE grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between LYNPARZA (olaparib) and decreases in hemoglobin has been demonstrated (See 7 Hematologic). Other hematological toxicities were generally CTCAE grade 1 or 2, however, there were reports of CTCAE grade 3 and higher events.

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the upper limit of normal was approximately 68%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Myelodysplastic syndrome/Acute myeloid leukemia (MDS/AML)

In clinical studies, across all indications and formulations, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and <1.5% at any time after starting LYNPARZA, including cases actively solicited during the long term follow up for overall survival.

In patients with *BRCAm* platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with LYNPARZA treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8.2% in patients receiving LYNPARZA and 4.0% in patients receiving placebo at a follow-up of 5 years. In the LYNPARZA arm, 9 out of 16 MDS/AML cases occurred after discontinuation of LYNPARZA during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the LYNPARZA arm and late onset of MDS/AML (See 8.2 Clinical Trial Adverse Reactions, SOLO2).

The risk of MDS/AML remains < 1.5% at 5 year follow up in the maintenance setting when