NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LYNPARZA® 150 mg film-coated Tablets
LYNPARZA® 100 mg film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 150 mg film-coated tablet contains 150 mg of olaparib.
Each 100 mg film-coated tablet contains 100 mg of olaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The LYNPARZA 150 mg tablet is a green to green/grey, oval, bi-convex tablet, 14.5 mm x 7.25 mm, debossed with 'OP150' on one side and plain on the reverse.

The LYNPARZA 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet, 14.5 mm x 7.25 mm, debossed with 'OP100' on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ovarian Cancer

LYNPARZA is indicated as monotherapy for the:

- maintenance treatment of adult patients with newly diagnosed 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

- maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

Breast Cancer

LYNPARZA is indicated as monotherapy for the

- treatment of adult patients with germline *BRCA*-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Important Administration Information

LYNPARZA is also available as a 50 mg capsule. DO NOT substitute LYNPARZA tablets (100 mg and 150 mg) with LYNPARZA capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Refer to the Data Sheet for LYNPARZA capsules for specific capsule dosing.

Maintenance treatment of newly diagnosed advanced ovarian cancer:

Patients must have confirmation of a breast cancer susceptibility gene (*BRCA)* mutation (identified by either germline or tumour testing) before Lynparza treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method.

Metastatic HER2-negative breast cancer:

Patients must have confirmation of a *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated. Germline *BRCA* mutation (*gBRCAm)* status should be determined by an experienced laboratory using a validated test method.

Dosage in adults

LYNPARZA is available as 100 mg and 150 mg tablets.

The recommended dose of LYNPARZA is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reduction.

Duration of treatment

Maintenance treatment of newly diagnosed advanced ovarian cancer: patients with advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer 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.

Platinum-sensitive relapsed ovarian cancer and metastatic HER2-negative breast cancer: For patients with either platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer or germline *BRCA*-mutated HER2-negative metastatic breast cancer, it is recommended that treatment be continued until progression of the underlying disease. There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

Missing dose

If a patient misses a dose of LYNPARZA, they should take their next normal dose at its scheduled time.

Dose adjustments

For adverse events

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea and anaemia, and dose reduction can be considered.

Gastrointestinal toxicities are frequently reported with olaparib therapy (see section 4.8) and are generally low grade (CTCAE grade 1 or 2) and intermittent. In addition to dose interruption or reduction, concomitant medicinal products (e.g. antiemetic therapy) may also be considered. Antiemetic prophylaxis is not required.

The recommended dose reduction is to 250 mg (one 150 mg tablet and one 100 mg tablet) twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduce to 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) is recommended.

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 LYNPARZA dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended LYNPARZA dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) (see sections 4.4 and 4.5).

Special patient populations

Children or adolescents

LYNPARZA is not indicated for use in paediatric patients, as safety and efficacy of LYNPARZA in children and adolescents have not been established.

Elderly (>65 years)

No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and over.

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 - 50 ml/min) the recommended dose of LYNPARZA is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 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 section 5.2).

Hepatic impairment

LYNPARZA can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see section 5.2). 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.

Non-Caucasian patients

There are limited clinical data available in non-Caucasian patients. However, no dose adjustment is required on the basis of ethnicity (see section 5.2).

Patients with performance status 2 to 4

There are very limited clinical data available in patients with performance status 2 to 4.

Method of administration

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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance (olaparib) or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haematological toxicity

Haematological toxicity occurs commonly in patients treated with LYNPARZA. While the majority were generally mild or moderate (CTCAE Grade 1 or 2), Grade 3 or higher events of anaemia (decrease in haemoglobin) occurred in 7.4% of patients in Study 19, and one patient died from a haemorrhagic stroke associated with thrombocytopenia. Patients should not start treatment with LYNPARZA until they have recovered from haematological toxicity caused by previous anti-cancer therapy (haemoglobin, 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 (see section 4.8).

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with LYNPARZA should be interrupted and appropriate haematological 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.

Myelodysplastic Syndrome/Acute Myeloid Leukaemia

The incidence of MDS/AML in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow-up, was <1.5%, with higher incidence in patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see section 4.8). 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 germline *BRCA* mutation (*gBRCAm)* 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 are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately.

Pneumonitis

Pneumonitis has been reported in <1.0% patients treated with LYNPARZA monotherapy in clinical studies. 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 dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, LYNPARZA treatment should be interrupted and prompt investigation

initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 300 mg twice daily.

LYNPARZA should not be taken during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a foetus. 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 (see section 4.6).

Breast-feeding

The excretion of olaparib in milk has not been studied in animals or in breast-feeding mothers. Breast-feeding mothers are advised not to breast-feed during treatment with LYNPARZA and for one month after receiving the last dose of LYNPARZA (see section 4.6).

Interactions with other medicinal products

Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended (see section 4.5). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2).

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 section 4.5).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Clinical studies of olaparib in combination with other anticancer 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 anticancer agents.

Effect of other drugs on olaparib

<u>Strong and moderate CYP3A inhibitors</u>

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Co-administration of olaparib with a strong CYP3A inhibitor (itraconazole) increased olaparib C_{max} by 42% and increased AUC by 170%. Therefore, concomitant use of itraconazole as well as other strong CYP3A inhibitors such as, but not limited to clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, and boceprevir is not recommended with LYNPARZA (see section 4.4).

Physiologically-based pharmacokinetic (PBPK) modelling has shown that moderate inhibitors will alter the clearance of olaparib and therefore concomitant use of moderate CYP3A inhibitors such as, but not limited to ciprofloxacin, erythromycin, diltiazem, fluconazole and verapamil is not recommended with LYNPARZA (see section 4.4).

If strong or moderate CYP3A inhibitors must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2).

Patients should avoid star fruit, grapefruit and Seville oranges while on LYNPARZA therapy as these foods are known to inhibit CYP3A enzymes.

Strong and moderate CYP3A inducers

Co-administration of olaparib with a strong CYP3A inducer (rifampicin) decreased olaparib C_{max} by 71% and AUC by 87%. It is therefore possible that CYP3A inducers could substantially diminish the clinical efficacy of LYNPARZA and as such concomitant use of strong inducers such as, but not limited to phenytoin, rifabutin, rifampin (rifampicin), carbamazepine, nevirapine, phenobarbital and St John's Wort (Hypericum perforatum) is not recommended with LYNPARZA (see section 4.4).

PBPK modelling has shown that moderate CYP3A inducers will decrease olaparib AUC by approximately 60% and therefore concomitant use of moderate CYP3A inducers such as, but not limited to bosentan, efavirenz, etravirine and modafinil is not recommended with LYNPARZA. If a moderate CYP3A inducer must be co-administered, the prescriber should be aware of a potential for decreased efficacy of LYNPARZA (see section 4.4).

Effect of olaparib on other drugs

CYP Interactions

Both induction and inhibition of CYP3A4 has been shown *in vitro*, however, PBPK simulations and clinical data suggest that the net effect of olaparib *in vivo* is weak inhibition of CYP3A. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, sirolimus, tacrolimus and quetiapine) are combined with LYNPARZA. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with LYNPARZA.

Induction of CYP1A2 and 2B6 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. Therefore, LYNPARZA upon co-administration may reduce the exposure to substrates of these metabolic enzymes.

Drug transporter interactions

Olaparib has also been shown to be an *in vitro* inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown, however, it cannot be excluded that LYNPARZA may increase the exposure to substrates of OATP1B1 (e.g. bosentan, glibenclamide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin and cisplatin) and MATE2K (e.g. metformin). In particular, caution should be exercised if LYNPARZA is administered in combination with any statin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D

LYNPARZA should not be used during pregnancy due to the teratogenic and genotoxic potential of olaparib. Female partners of male patients taking LYNPARZA should also avoid pregnancy. No studies have been conducted in pregnant women.

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. Studies in rats have shown that olaparib causes embryofetal lethality and induces major fetal malformations (major eye and vertebral/rib malformations) at exposures below those expected at the recommended human dose of 300 mg twice daily.

If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be informed of the potential hazard to the foetus or potential risk of loss of the pregnancy (see section 4.4).

Contraception and pregnancy testing

Women of child-bearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of LYNPARZA (see section 4.4). 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.

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. Female partners of male patients must also use effective contraception if they are of childbearing potential (see section 4.4). Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA.

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 receiving the last dose.

Effects on fertility

Olaparib had no effect on fertility in male rats. In a female fertility study in rats, extended oestrus was observed in some animals although mating performance and fertility was not affected. Embryofoetal survival was reduced in this study. Exposures achieved in these studies were subclinical and the full effects on fertility may not have been revealed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies to establish the effects of olaparib on the ability to drive and use machines have been conducted. However, during treatment with LYNPARZA, asthenia, fatigue, and dizziness have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 UNDESIRABLE EFFECTS

Overall Summary of Adverse Drug Reactions

LYNPARZA monotherapy has been associated with laboratory findings and/or clinical diagnoses generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation.

Tabulated List of Adverse Drug Reactions from Clinical Trials

The safety profile is based on pooled data from 2901 patients with solid tumours treated with LYNPARZA monotherapy in clinical trials at the recommended dose.

The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organised by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. 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 1 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
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Myelodysplastic syndrome/Acute myeloid leukaemia	Uncommon	Uncommon
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Very common	Common
	Lymphopenia[a]	Common	Uncommon
Immune system disorders	Hypersensitivity[a]	Uncommon	-
	Angioedema[*]	Uncommon	
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia	Very common	-
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Common
	Nausea	Very common	Common
	Dyspepsia	Very common	-
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Very common	Uncommon
Skin and subcutaneous tissue disorders	Rash[a]	Common	Rare-
	Dermatitis[a]	Uncommon	-
	Erythema nodosum	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Increase in blood creatinine	Common	Uncommon
	Mean corpuscular volume elevation	Uncommon	-

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased; Neutropenia includes PTs of of agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased; Thrombocytopenia includes PTs of platelet count decreased, platelet production decreased, plateletcrit decreased and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative. Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.

[*] As observed in post-marketing setting

Description of selected adverse reactions

Myelodysplastic syndrome/Acute myeloid leukaemia

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

In patients with *BRCA*m 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 olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% in patients receiving olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains < 1.5% at 5 year follow up in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years.

Haematological toxicity

Anaemia and other haematological toxicities are generally low grade (CTCAE grade 1 or 2), however, there are reports of CTCAE grade 3 and higher events. Anaemia 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 olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with LYNPARZA the incidence of CTCAE grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 20%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low to 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.

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 which may require dose interruption or reduction and/or further treatment (see sections 4.2 and 4.4).

Other laboratory findings

In clinical studies with LYNPARZA the incidence of CTCAE grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 10%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. Ninety percent (90%) of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of LYNPARZA treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of LYNPARZA treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

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.

Contact the National Poisons Centre on 0800 POISON (0800 764 766) for advice on management.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological actions

Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines *in vitro* and tumour growth in mice either as a standalone treatment or in combination with established chemotherapies.

PARP enzymes are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells, this also leads to the formation of DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional *BRCA*1 and 2 genes, is effective at repairing these DNA DSBs.

In cancers that lack functional components of HRR, such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of *BRCA1* or *BRCA2* mutations, HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

In *BRCA*-deficient animal models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone that correlated with the period of olaparib maintenance treatment.

There was no correlation between the dose and degree of PARP-1 inhibition observed in the pharmacodynamic studies, with maximal inhibition achieved at relatively low doses. Therefore, the dose selection was based upon the higher clinical response rates observed at higher doses.

Clinical efficacy and safety

Maintenance treatment of newly diagnosed advanced ovarian cancer

SOLO1 Study (D0816C00001) in newly diagnosed advanced patients with a BRCA mutation

SOLO1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in advanced (FIGO Stage III-IV) high-grade serous or endometrioid *BRCA*-mutated (*BRCAm*) ovarian cancer. The study randomised 391 patients (2:1 randomisation: 260 olaparib and 131 placebo) who were in response (CR [complete response] or PR [partial response]) following completion of first-line platinum-containing chemotherapy. Patients were stratified by response to first-line platinum chemotherapy (CR or PR). Treatment was continued for 2 years or until progression of the underlying disease. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease that remained stable (i.e. no evidence of disease progression) could continue to receive Lynparza beyond 2 years. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or central test (i.e. Myriad Integrated BRAC*Analysis*® test, Myriad BRACAnalysis CDx®, China BGI test) or from testing a tumour sample using a local test. The *BRCAm* status of all patients was confirmed where possible using the Myriad Integrated BRAC*Analysis*® test, the Myriad BRACAnalysis CDx® or the Foundation Medicine FoundationOne CDx™ Clinical Trial Assay.

There were 389 patients who were germline *BRCAm* and 2 who were somatic *BRCAm* in SOLO1.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo treatment arms. Median age was 53 years in both arms. Ovarian cancer was the primary tumour in 85% of the patients. The most common histological type was serous (96%), endometrioid histology was reported in 2% of the patients. Most patients were ECOG performance status 0 (78%). All patients had received first-line platinum-based therapy; response to prior platinum chemotherapy was complete in 82% and partial in 18% of the patients. Ninety three percent (93%) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to the date of randomisation, until objective radiological disease progression.

The study demonstrated a clinically relevant and statistically significant improvement in investigator assessed PFS for olaparib compared to placebo, with a hazard ratio (HR) of 0.30 (95% CI 0.23 – 0.41; p< 0.0001; the median was not reached for olaparib versus 13.8 months for placebo). Based on Kaplan -Meier estimates, the proportion of patients that were progression free at 12, 24 and 36 months were 88%, 74%, and 60% for olaparib versus 51%, 35% and 27% for placebo; the median follow-up time was 41 months for both the olaparib and placebo treatment arms. The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS (HR 0.28; 95% CI 0.20-0.39; p< 0.0001; median not reached for olaparib vs. 14.1 months for placebo). A clinically meaningful and

statistically significant improvement in PFS2 was also observed with a HR of 0.50 (95% CI 0.35-0.72; p=0.0002; median not reached for olaparib vs. 41.9 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies (see Table 2).

At the time of PFS analysis, interim OS data were immature with events in 82/391 (21%) patients (HR 0.95; 95% CI 0.60-1.53; p=0.8903; medians not reached). A clinically meaningful and statistically significant improvement in TFST was observed for olaparib-treated patients (Table 2).

Table 2 Summary of key efficacy findings for newly diagnosed patients with *BRCA*-mutated advanced ovarian cancer in SOLO1

	Olaparib 300 mg bd	Placebo
PFS (51% maturity)		
Number of events: Total number of patients (%)	102:260 (39)	96:131 (73)
Median time (months)	NR	13.8
Progression-free at 12 months (%)[a]	88	51
Progression-free at 24 months (%)[a]	74	35
Progression-free at 36 months (%)[a]	60	27
HR (95% CI)[b]	0.30 (0.23-0.41)	
P value (2-sided)	p<0.0001	
PFS2 (31% maturity)		
Number of events: Total number of patients (%)	69:260 (27)	52:131 (40)
Median time (months)	NR	41.9
HR (95% CI)[b]	0.50 (0.35-0.72)	
P value (2-sided)	p=0.0002	
Interim OS (21% maturity)		
Number of events: Total number of patients (%)	55:260 (21)	27:131 (21)[c]
Median time (months)	NR	NR
HR (95% CI)[b]	0.95 (0.60-1.53)	
P value (2-sided)	p=0.8903	
TFST		
Number of events: Total number of patients (%)	99:260 (38)	94:131 (72)
Median time (months)	51.8	15.1
HR (95% CI)[b]	0.30 (0.22-0.40)	
P value[*] (2-sided)	p<0.0001	

[a] Kaplan-Meier estimates.

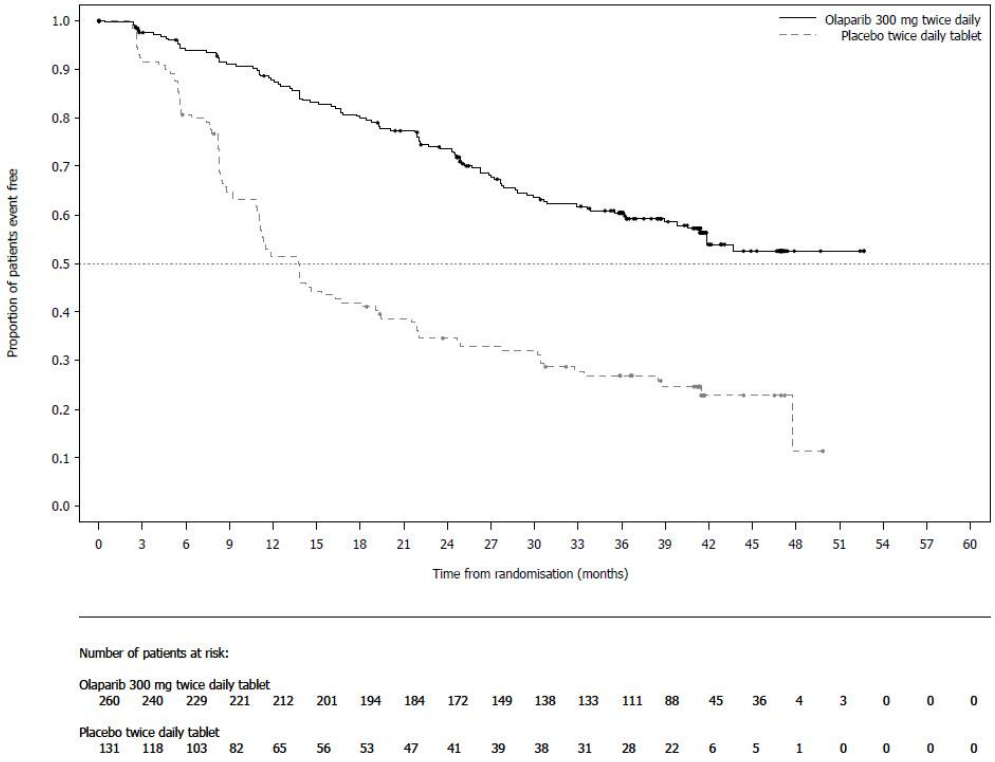
[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model including response to previous platinum chemotherapy (CR or PR) as a covariate.

[c] Of the 94 patients on the placebo arm who received subsequent therapy, 49 (52%) received a PARP inhibitor.

[*] Not controlled for multiplicity.

bd Twice daily; NR not reached; CI Confidence interval

Figure 1 SOLO1: Kaplan-Meier plot of PFS for newly diagnosed patients with *BRCAm* advanced ovarian cancer (51% maturity - investigator assessment)



There was no decrease in HRQoL from baseline for olaparib-treated patients over the 24-month treatment period and no clinically relevant differences in HRQoL compared with placebo-treated patients as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Platinum sensitive relapsed (PSR) ovarian cancer

The efficacy of LYNPARZA in the maintenance treatment setting in platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer is supported by 2 randomised, double-blind, placebo-controlled trials in patients with PSR and *BRCA*-mutated disease (SOLO2) and in patients with PSR disease (Study 19). In both studies, PSR patients who were in response following completion of platinum-based chemotherapy and whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRAC*Analysis*® test or from testing a tumour sample using a local test or a test performed by Foundation Medicine.

SOLO2 Study (D0816C00002) in PSR patients with a BRCA mutation

The study compared the efficacy of LYNPARZA 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 randomisation: 196 olaparib and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy. All patients had evidence of germline *BRCA* mutation (*gBRCAm*) at baseline.

The primary endpoint was PFS determined by investigator assessment using RECIST 1.1. Secondary efficacy endpoints included PFS2; OS, TDT, TFST, TSST; and HRQoL.

The study met its primary objective demonstrating a clinically meaningful and statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a HR of 0.30 (95% CI 0.22-0.41; p<0.0001; median 19.1 months for olaparib vs. 5.5 months for placebo). 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 olaparib vs. 5.5 months for placebo). At 2 years, 43% olaparib-treated patients remained progression-free compared with only 15% placebo-treated patients. A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0.50 (95% CI 0.34-0.72; p=0.0002; median not reached for olaparib vs. 18.4 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. At the final analysis of OS (61% maturity) the HR was 0.74 (95% CI 0.54-1.00; p=0.0537; median 51.7 months for olaparib vs 38.8 months for placebo) which did not reach statistical significance.

Clinically meaningful and statistically significant improvements in TDT, TFST and TSST were also observed for olaparib-treated patients (Table 3).

A summary of key efficacy findings for patients with *gBRCAm* PSR ovarian cancer in SOLO2 is presented in Table 3.

Table 3 Summary of key efficacy findings for patients with *gBRCAm* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	**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	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months)	NR	18.4
HR (95% CI) [a]	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	
OS (61% maturity)		
Number of events: Total number of patients (%)	116:196 (59)	65:99 (66)[b]
Median time (95% CI), months	51.7 (41.5, 59.1)	38.8 (31.4,48.6)
HR (95% CI) [a]	0.74 (0.54-1.00)	
P value (2-sided)	p=0.0537	
TFST		
Number of events: Total number of patients (%)	92:196 (47)	79:99 (80)
Median time (months)	27.9	7.1
HR (95% CI) [a]	0.28 (0.21-0.38)	
P value* (2-sided)	p<0.0001	
TDT		
Number of events: Total number of patients (%)	112:196 (57)	86:99 (87)
Median time (months)	19.4	5.6
HR (95% CI) [a]	0.31 (0.23-0.42)	
P value* (2-sided)	p<0.0001	
TSST		
Number of events: Total number of patients (%)	68:196 (35)	60:99 (61)
Median time (months)	NR	18.2
HR (95% CI) [a]	0.37 (0.26-0.53)	
P value* (2-sided)	p<0.0001	

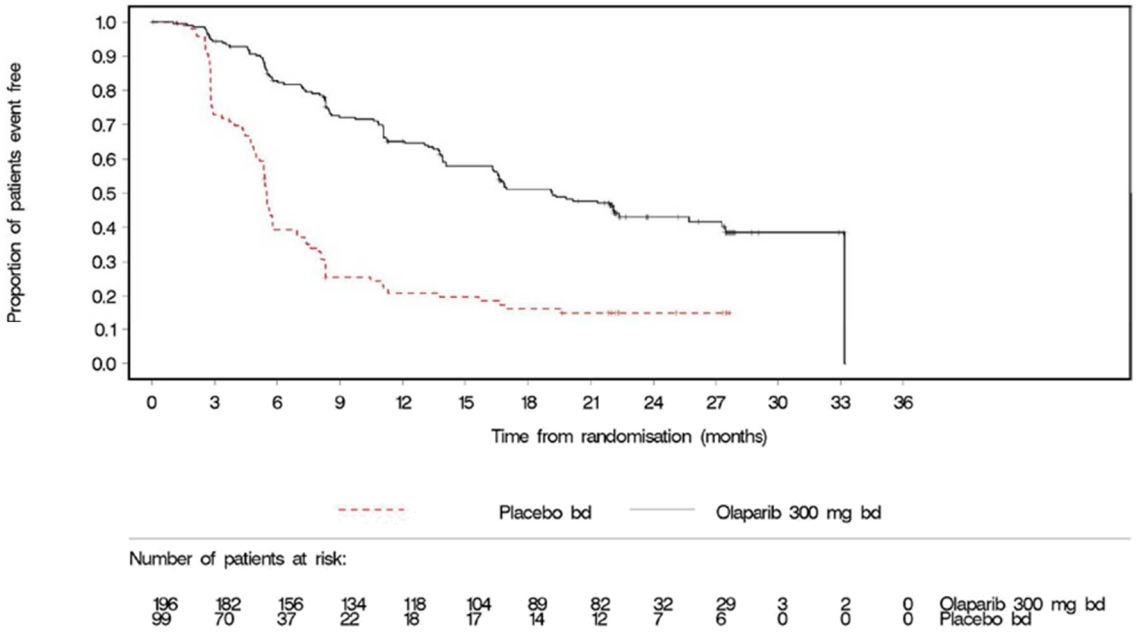
* Not controlled for multiplicity

[a] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazard model including 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 as covariates.

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

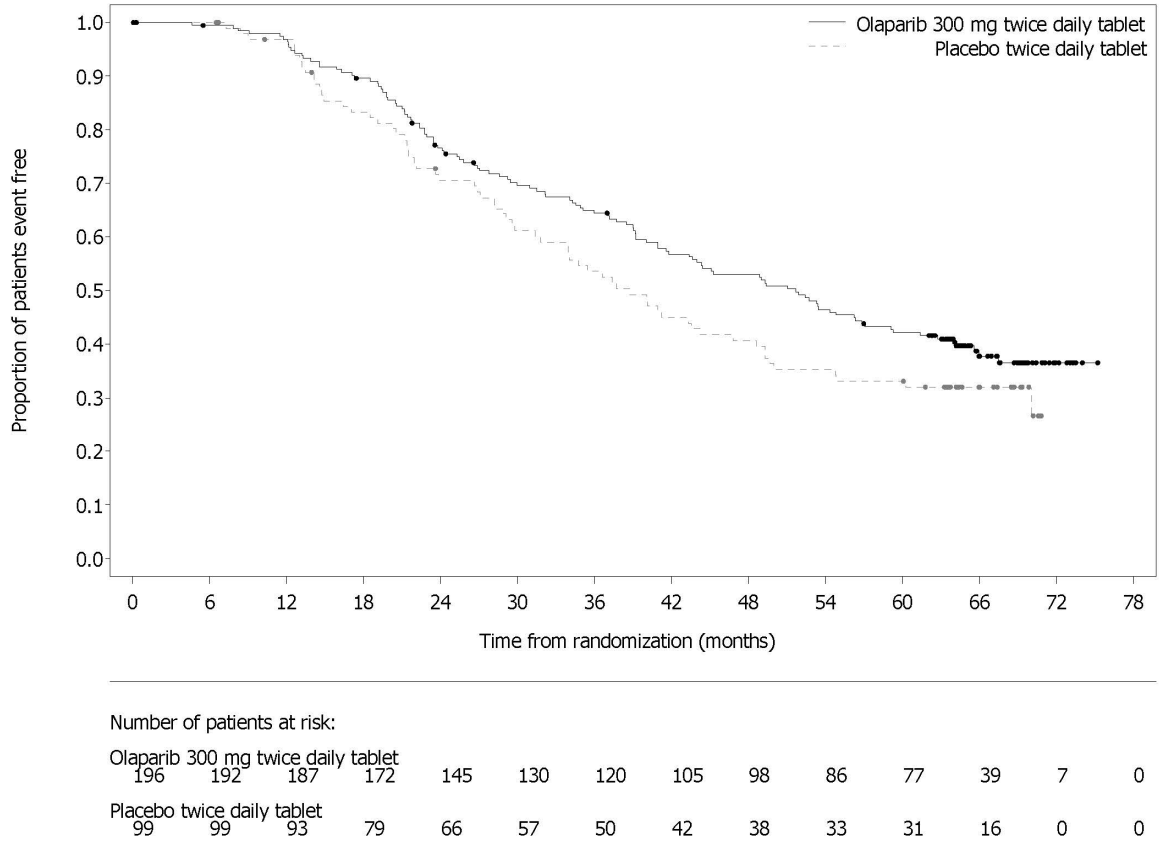
bd Twice daily; NR Not Reached; OS overall survival; PFS Progression-free survival; CI Confidence interval; TDT Time from randomisation to discontinuation of treatment or death; TFST Time from randomisation to start of first subsequent therapy or death; PFS2 Time from randomisation to second progression; TSST Time from randomisation to start of second subsequent therapy or death.

Figure 2 SOLO2: Kaplan-Meier plot of PFS in patients with gBRCAm PSR ovarian cancer (63% maturity - investigator assessment)



bd Twice daily; PFS Progression-free survival

Figure 3 SOLO2: Kaplan-Meier plot of OS in patients with gBRCAm PSR ovarian cancer (61% maturity)



There was no difference between olaparib and placebo treatment groups in HRQoL as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) over 12 months (estimated difference -0.03; 95% CI: -2.191, 2.2126; p= 0.9765).

Study 19 (D0810C00019) in PSR patients

The study compared the efficacy of LYNPARZA capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken to progression with placebo 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 PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS (overall survival), DCR (disease control rate) defined as confirmed CR/PR + SD (stable disease), HRQoL (health related quality of life), and disease related symptoms. Exploratory analyses of time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) were also performed.

The study met its primary objective demonstrating a statistically significant and clinically relevant improvement in PFS for olaparib compared with placebo with a HR 0.35 (95% CI 0.25-0.49; p<0.00001; median 8.4 months olaparib vs 4.8 months placebo). At the final analysis (data cut off [DCO] 9 May 2016) for OS at 79% maturity, the HR comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; p=0.02138 [did not meet pre-specified significance level of < 0.0095]; median 29.8 months olaparib versus 27.8 months placebo). TFST and TSST were also longer for olaparib-treated patients (Table 4)

Preplanned subgroup analysis identified patients with *BRCA*-mutated ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. There were no multiplicity strategies in place for the sub-group analyses.

In *BRCA*-mutated patients the HR for PFS improvement was 0.18 (95% CI 0.10-0.31; p<0.00001; median 11.2 months for olaparib vs 4.3 months for placebo). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0.62 (95% CI 0.42-0.93; p=0.02140; median 34.9 months versus 30.2 months for placebo). In the olaparib-treated group, 28.4% of patients remained on treatment for ≥2 years and 14.9% for ≥5 years. In the placebo-treated group, 8.1% of patients remained on treatment for ≥2 years and 1.6% for ≥5 years. TFST and TSST were also longer for olaparib-treated patients (Table 4).

A summary of key efficacy findings for all patients and patients with *BRCA*-mutated PSR ovarian cancer in Study 19 is presented in Table 4.

Table 4 Summary of key efficacy findings for all patients and patients with *BRCAm* PSR ovarian cancer in Study 19

	All patients		***BRCA*-mutated**	
	Olaparib 400 mg capsule bd	**Placebo**	**Olaparib 400 mg capsule bd**	**Placebo**
PFS – DCO 30 June 2010				
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)
Median time (months)	8.4	4.8	11.2	4.3
HR (95% CI)[a]	0.35 (0.25-0.49)		0.18 (0.10–0.31)	
P value[*] (2-sided)	p<0.00001		p<0.00001	
OS - DCO 09 May 2016				
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81)[b]
Median time (months)	29.8	27.8	34.9	30.2
HR (95% CI)[a]	0.73 (0.55–0.95)		0.62 (0.42–0.93)	
P value* (2-sided)	p=0.02138		p=0.02140	
TFST – DCO 09 May 2016				
Number of events: Total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)
Median time (months)	13.3	6.7	15.6	6.2
HR (95% CI)[a]	0.39 (0.30-0.52)		0.33 (0.22–0.49)	
P value* (2-sided)	p<0.00001		p<0.00001	
TSST – DCO 09 May 2016				
Number of events: Total number of patients (%)	104:136 (77)	119:128 (93)	53:74 (72)	56:62 (90)
Median time (months)	19.1	14.8	21.4	15.3
HR (95% CI)[a]	0.53 (0.40-0.69)		0.43 (0.29-0.64)	
P value* (2-sided)	p<0.00001		p= 0.00003	

* There were no multiplicity strategies in place for the sub-group analyses or for the All patients TFST and TSST.

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

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

bd Twice daily; OS Overall survival; PFS Progression-free survival; DCO Data cut off; CI Confidence interval; TFST Time from randomisation to start of first subsequent therapy or death; TSST Time from randomisation to start of second subsequent therapy or death.

Within the overall population, the disease control rate (DCR) at 24 weeks was 53% and 25% for patients in the olaparib and placebo groups, respectively and in the *BRCA*-mutated population DCR was 57% and 24% for patients in the olaparib and placebo groups, respectively.

No statistically significant differences were observed between treatment groups in patient reported symptoms or HRQoL.

Germline BRCA-mutated (gBRCAm) HER2-negative metastatic breast cancer

OlympiAD (Study D0819C00003) in HER2-negative metastatic breast cancer patients with a gBRCA mutation

The study was a Phase III randomised, open-label, controlled trial that compared the efficacy of olaparib (300 mg [2 x 150 mg tablets] twice daily) taken to progression with a comparator arm of physician's choice of chemotherapy (capecitabine, eribulin, or vinorelbine). In the study 302 patients with *gBRCAm* HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease were randomised (2:1 randomisation: 205 olaparib and 97 comparator). Patients were stratified based on: receipt of prior chemotherapy regimens for metastatic breast cancer, oestrogen receptor (ER) and / or progesterone receptor (PgR) positive vs ER and PgR negative, prior platinum for breast cancer. The primary endpoint was PFS assessed by BICR using RECIST 1.1. Secondary endpoints included PFS2, OS, objective response rate (ORR) and HRQoL.

All patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the neo adjuvant, adjuvant or metastatic setting. Prior therapy with platinum for metastatic breast cancer was allowed provided there had been no evidence of disease progression during platinum treatment. Prior therapy with platinum in the (neo) adjuvant setting was allowed provided the last dose was received at least 12 months prior to randomisation. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients with ER and/or PgR 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 had tumour assessments at baseline and every 6 weeks for the first 24 weeks, and then every 12 weeks relative to date of randomisation, until objective radiological disease progression.

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS for olaparib-treated patients compared with those in the comparator arm with a HR of 0.58 (95% CI 0.43-0.80; p=0.0009; median 7.0 months for olaparib vs. 4.2 months for comparator) (Table 5).

A clinically meaningful and 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 olaparib vs 9.3 months for comparator) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. In the measurable disease patient population (77%), ORR in olaparib-treated patients was 60% (95% CI 52.0-67.4) and in patients who received comparator was 29% (95% CI 18.3-41.3). The median time to onset of

response was 47 days for olaparib vs 45 days for comparator. The median duration of response was 6.4 months for olaparib vs 7.1 months for comparator. Overall survival was 64% mature at the time of the final OS analysis (DCO 25 September 2017). The OS HR comparing olaparib with comparator was 0.90 (95% CI 0.66-1.23; p=0.5131; median 19.3 months for olaparib vs. 17.1 months for comparator). The median follow-up time in censored patients was 25.3 months for olaparib vs 26.3 months for comparator.

Consistent results were observed across patient subgroups.

Table 5 Summary of key efficacy findings for patients with *gBRCAm* HER2-negative metastatic breast cancer in OlympiAD

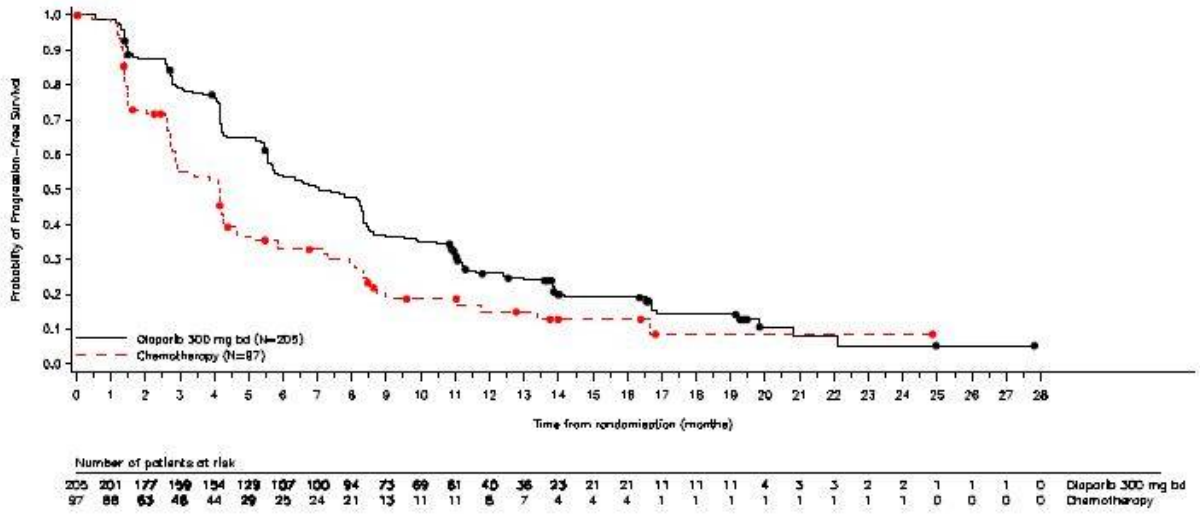
	Olaparib 300 mg bd	**Physician's choice chemotherapy[a]**
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months)	7.0	4.2
HR (95% CI)		0.58 (0.43-0.80)
P value (2-sided)		p=0.0009
PFS2 (52% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	104:205 (51)	53:97 (55)
Median time (months)	13.2	9.3
HR (95% CI)		0.57 (0.40-0.83)
P value (2-sided)		p=0.0033
OS (64% maturity) – DCO 25 September 2017		
Number of events: Total number of patients (%)	130:205 (63)	62:97 (64)[b]
Median time (months)	19.3	17.1
HR (95% CI)		0.90 (0.66-1.23)
P value (2-sided)		p=0.5131
ORR – DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)	100/167 (60)	19/66 (29)
95% CI	52.0 to 67.4	18.3 to 41.3
Complete response (%)	15:167 (9)	1:66 (2)
Partial response (%)	85:167 (51)	18:66 (27)

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

bd Twice daily; CI Confidence interval; DCO Data cut off; HR Hazard ratio; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PFS2 Time to second progression or death.

Figure 4 OlympiAD: Kaplan-Meier plot of PFS in patients with *gBRCAm* HER2-negative metastatic breast cancer (77% maturity)



A significant difference in global health status/QoL (assessed using the EORTC QLQ-C30 questionnaire which uses a 0-100 point scale) in favour of olaparib was observed (adjusted mean difference in change from baseline score was 7.5 points [95% CI: 2.48-12.44; p=0.0035]). Time to deterioration (≥10 points decrease from baseline) in global health status/QoL score was statistically significantly longer on the olaparib arm (HR 0.44; 95% CI: 0.25-0.77; p = 0.0043; median not reached for olaparib vs. 15.3 months for comparator arm). Over the treatment period, the proportion of patients with clinically significant improvement (≥10 points increase from baseline) in global health status/QoL score was 33.7% (n=69) in the olaparib arm and 13.4% (n=13) in the comparator arm.

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 twice daily multiple dosing of olaparib .

Retreatment on relapse

There are no data to support retreatment with olaparib as maintenance following subsequent relapse.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics

Olaparib displays high inter-patient variability in PK parameters, including C_{max}, AUC, Vd and CL/F.

The pharmacokinetics of olaparib at the 300 mg tablet dose are characterised 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.

Absorption

Following oral administration of olaparib via the tablet formulation (2 x 150 mg), absorption is rapid with 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 section 4.2).

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 ^{14}C-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 fluorophenyl 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-opened piperazin-3-ol moiety, and two mono-oxygenated metabolites (each~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of clinical importance. Based on evaluation using enzyme activity, olaparib was not an inducer of CYP2C9 or 2C19. *In vitro*, olaparib is a substrate of and inhibits the efflux transporter P-gp (IC_{50} = 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.

Excretion

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 faeces. The majority of the material was excreted as metabolites.

Special populations

In population based PK analyses, patient age, bodyweight or race (including White and Japanese patients) were not significant covariates.

Effect on Renal Impairment

Following a single oral 300 mg dose of olaparib 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 olaparib 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 adjustment is recommended for patients with moderate renal impairment (see section 4.2).

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

Effect of Hepatic Impairment

Following a single oral 300 mg dose of olaparib to patients with mild hepatic impairment (Child-Pugh classification A) AUC increased by 15% and C_{max} by 13% and to patients with moderate hepatic impairment (Child-Pugh classification B) AUC increased by 8% and C_{max} decreased by 13% compared with patients with normal hepatic function. No LYNPARZA dose adjustment is required in patients with mild or moderate hepatic impairment (see section 4.2).

Olaparib has not been studied in patients with severe hepatic impairment (Child-Pugh classification C).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Olaparib showed no mutagenic potential in bacterial cells, but was clastogenic in mammalian cells *in vitro*. When dosed orally to rats, olaparib induced micronuclei in bone marrow. This clastogenicity is consistent with the primary pharmacology of olaparib and indicates potential for genotoxicity in man.

Repeat dose toxicity

In repeat-dose toxicity studies of up to 6 months duration in rats and dogs, daily oral doses of olaparib were well-tolerated. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. These findings occurred at exposures below those seen clinically and were largely reversible within 4 weeks of cessation of dosing. Studies using human bone marrow cells also showed that direct exposure to olaparib can result in toxicity to bone marrow cells in *ex vivo* assays.

Reproductive toxicology

Olaparib had no effect on fertility in male rats. In a female fertility study in rats, extended oestrus was observed in some animals although mating performance and fertility was not affected. Embryofoetal survival was reduced in this study.

In rat embryofoetal development studies, olaparib caused reduced embryofoetal survival, reduced foetal weight and foetal developmental abnormalities (including visceral and skeletal abnormalities, and major eye and vertebral/rib malformations) at dose levels that did not induce significant maternal toxicity.

Carcinogenicity

Carcinogenicity studies have not been conducted with olaparib.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Core

- Copovidone
- Colloidal silicon dioxide
- Mannitol
- Sodium stearyl fumarate

Tablet coating

- Hypromellose
- Macrogol 400
- Titanium dioxide (E171)
- Iron oxide yellow (E172)
- Iron oxide black (E172) (150 mg tablet only)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

4 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Alu/Alu non-perforated blister containing 8 tablets. Cartons of 56 tablets (7 blisters).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

9 DATE OF FIRST APPROVAL

15 August 2019

10. DATE OF REVISION OF TEXT

5 February 2021

LYNPARZA is a registered trademark of the AstraZeneca group of companies.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Erythema nodosum added to Table 1