

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LYNPARZA® 50 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50 mg of olaparib

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

White, opaque, size 0 hard capsule, marked with "OLAPARIB 50 mg" and the AstraZeneca logo in black ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Olaparib is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed *BRCA*-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

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 100mg and 150 mg tablet. DO NOT substitute LYNPARZA capsules (50 mg) with LYNPARZA tablets (100 mg and 150 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 tablets for specific tablet dosing.

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

Dosage in adults

The recommended dose of LYNPARZA is 400 mg (eight 50 mg capsules) taken twice daily, equivalent to a total daily dose of 800 mg.

LYNPARZA should be taken on an empty stomach (at least 1 hour after a meal). The capsules should not be opened. Once LYNPARZA is taken, refrain from eating for 2 hours.

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 200 mg twice daily (equivalent to a total daily dose of 400 mg). If a further dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 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 150 mg taken twice daily (equivalent to a total daily dose of 300 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended LYNPARZA dose reduction is to 200 mg taken twice daily (equivalent to a total daily dose of 400 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.

Use in men

LYNPARZA is not indicated for use in men, as safety and efficacy of LYNPARZA in men 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 300 mg twice daily (equivalent to a total daily dose of 600 mg). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance \leq 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.

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 \leq 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 *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 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 400 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 (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

Elimination of olaparib is likely to be independent of formulation, therefore the tablet drug interaction and organ impairment findings (section 5.2) have been extrapolated to inform LYNPARZA capsule dose adjustment (section 4.2).

Strong and moderate CYP3A inhibitors

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Co-administration of olaparib [tablet formulation] 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 telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir 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 it is a CYP3A inhibitor.

Strong and moderate CYP3A inducers

Co-administration of olaparib [tablet formulation] 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), rifapentine, 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 50% and therefore concomitant use of moderate CYP3A inducers such as, but not limited to bosentan, efavirenz, etravirine, modafinil and nafcillin 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, pimozide, 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, repaglinide, 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.

Food interactions

The effect of food on olaparib has been studied. Co-administration with food slowed the rate (T_{max} delayed by 2 hours) of absorption and increased the extent of absorption of olaparib (AUC increased by approximately 20%).

4.6 FERTILITY, PREGNANCY AND LACTATION

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. Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with LYNPARZA (see section 4.5).

Pregnancy

Category D

LYNPARZA should not be used during pregnancy due to the teratogenic and genotoxic potential of olaparib. 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 400 mg twice daily.

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

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Lymphopenia ^a	Common	Uncommon
Immune system disorders	Rash ^a	Common	Rare
	Hypersensitivity ^a	Uncommon	Rare
	Dermatitis ^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
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 ^a	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Uncommon
	Mean cell volume increased	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 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 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 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, tablet formulation, 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 (SOLO1, tablet formulation).

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 23%, absolute neutrophils 19%, platelets 6%, lymphocytes 29% 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 58%. 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 11%. 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 leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional *BRCA1* and 2 genes, is effective at repairing these DNA DSBs.

In the absence of functional *BRCA1* or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells. Thus, olaparib induces synthetic lethality in *BRCA1* and 2 mutated cancer cells.

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.

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

Platinum sensitive relapsed (PSR) ovarian cancer

The safety and efficacy of LYNPARZA as a maintenance therapy in the treatment of patients with PSR ovarian, fallopian tube or primary peritoneal cancer with a histology type of serous, or a serous component, following treatment with two or more platinum containing regimens, were studied in a Phase II randomised, double blind placebo controlled trial (Study 19). The study compared the efficacy of LYNPARZA maintenance treatment taken to progression with no maintenance treatment in 265 (136 LYNPARZA and 129 placebo) PSR patients who were in response (CR [complete response] or PR [partial response]) following completion of platinum containing chemotherapy. The primary endpoint was 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.

Only PSR patients who were in response following completion of platinum based chemotherapy and whose disease had recurred >6 months after completion of prior penultimate platinum based chemotherapy were enrolled. Patients could not have received prior LYNPARZA or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation.

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

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 ($n = 136$) there was a statistically significant improvement in PFS, TFST, and TSST. The median PFS improvement was 6.9 months over placebo (HR 0.18; 95% CI 0.10-0.31; $p < 0.00001$; median 11.2 months vs 4.3 months). At the final analysis (data cut off [DCO] 9 May 2016) the time from randomisation to start of first subsequent therapy or death (TFST) was 9.4 months longer for olaparib treated patients (HR 0.33; 95% CI 0.22– 0.49; $p < 0.00001$; median 15.6 months versus 6.2 months). The time from randomisation to start of second subsequent therapy or death (TSST) was 6.1 months longer for olaparib treated patients (HR 0.43; 95% CI 0.29- 0.64; $p = 0.00003$; median 21.4 months versus 15.3 months). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0.62 (95% CI 0.42-0.93; $p = 0.02140$; median 34.9 months versus 30.2 months). 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.

In the *gBRCA*-mutated subgroup ($n = 96$) there was a statistically significant improvement in PFS, TFST, and TSST. The median PFS improvement was 7.1 months over placebo (HR 0.17; 95% CI 0.09-0.31; $p < 0.00001$; median 11.2 months vs 4.1 months). At the final analysis (DCO 9 May 2016) the time from randomisation to start of first subsequent therapy or death (TFST) was 9.4 months longer for olaparib-treated patients (HR 0.32; 95% CI 0.20-

0.51; $p < 0.00001$; median 15.6 months versus 6.2 months). The time from randomisation to start of second subsequent therapy or death (TSST) was 4 months longer for olaparib treated patients (HR 0.44; 95% CI 0.28- 0.71; $p = 0.00086$; median 19.3 months versus 15.3 months). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0.68 (95% CI 0.42- 1.10; $p = 0.11363$; median 32.9 months versus 27.3 months). In the olaparib-treated group, 24.5% of patients remained on treatment for ≥ 2 years and 11.3% for ≥ 5 years. In the placebo-treated group, 7.0% of patients remained on treatment for ≥ 2 years and 2.3% for ≥ 5 years.

A summary of key efficacy findings for patients with *BRCA*-mutated and *gBRCA*-mutated PSR ovarian cancer in Study 19 is presented in Table 2.

Table 2 Summary of key efficacy findings for patients with *BRCA*-mutated and *gBRCA*-mutated PSR ovarian cancer in Study 19

	<i>BRCA</i> -mutated		<i>gBRCA</i> -mutated	
	Olaparib 400 mg bid n = 74	Placebo n = 62	Olaparib 400 mg bid n = 53	Placebo n = 43
PFS – DCO 30 June 2010				
Number of events: Total number of patients (%)	26:74 (35%)	46:62 (74%)	17:53 (32%)	33:43 (77%)
Median time (months)	11.2	4.3	11.2	4.1
HR (95% CI) ^a	0.18 (0.10–0.31)		0.17 (0.09-0.31)	
P value* (2-sided)	$p < 0.00001$		$p < 0.00001$	
Time to first subsequent therapy or death (TFST) – DCO 09 May 2016				
Number of events: Total number of patients (%)	55:74 (74%)	59:62 (95%)	38:53 (72%)	41:43 (95%)
Median time (months)	15.6	6.2	15.6	6.2
HR (95% CI) ^a	0.33 (0.22–0.49)		0.32 (0.20-0.51)	
P value* (2-sided)	$p < 0.00001$		$p < 0.00001$	
Time to second subsequent therapy or death (TSST) – DCO 09 May 2016				
Number of events: Total number of patients (%)	53:74 (72%)	56:62 (90%)	37:53 (70%)	38:43 (88%)
Median time (months)	21.4	15.3	19.3	15.3
HR (95% CI) ^a	0.43 (0.29–0.64)		0.44 (0.28-0.71)	
P value* (2-sided)	$p = 0.00003$		$p = 0.00086$	
OS – DCO 09 May 2016				
Number of events: Total number of patients (%)	49:74 (66%)	50:62 (81%) ^b	35:53 (66%)	34:43 (79%) ^b
Median time (months)	34.9	30.2	32.9	27.3
HR (95% CI) ^a	0.62 (0.42–0.93)		0.68 (0.42-1.10)	
P value (2-sided)	$p = 0.02140$		$p = 0.11363$	

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

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

- ^b Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%)⁶⁰ received a subsequent PARP inhibitor. Approximately a third of placebo-treated patients in the g*BRCA*-mutated subgroup (13/43; 30.2%) received a subsequent PARP inhibitor.
- N Number of events/number of randomised patients; bd Twice daily; HR Hazard ratio; 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 *BRCA*-mutated population the disease control rate at 24 weeks was 57% and 24% for patients in the LYNPARZA and placebo groups, respectively.

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

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 the LYNPARZA tablet formulation.

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, V_d and CL/F.

The pharmacokinetics of olaparib at the 400 mg twice daily capsule dose are characterised by an apparent plasma clearance of ~8.6 L/h, an apparent volume of distribution of ~167 L and a terminal half-life of 11.9 hours.

Absorption

Following oral administration of olaparib via the capsule formulation, absorption is rapid with peak plasma concentrations typically achieved between 1 to 3 hours after dosing. On multiple-dosing there is no marked accumulation, with steady state exposures achieved within ~3 to 4 days.

Food Effects

Co-administration with food slowed the rate (t_{max} delayed by 2 hours) and increased the extent of absorption of olaparib (AUC increased by approximately 20%). Consequently, patients should take LYNPARZA at least one hour after food, and should refrain from eating for 2 hours afterwards (see section 4.2).

Distribution

The *in vitro* plasma protein binding is approximately 82% at clinically relevant concentrations of 10 µg/mL.

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

Metabolism

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

Following oral dosing of ¹⁴C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively).

The metabolism of olaparib is extensive with the main site of metabolism being the piperazine and 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). Pharmacodynamic activity of the metabolites is unknown.

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

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 ¹⁴C-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 (tablet formulation) to patients with mild renal impairment (creatinine clearance: 51 to 80 mL/min), AUC increased by 24% and C_{max} by 15%

compared with patients with normal renal function. No LYNPARZA dose adjustment is required for patients with mild renal impairment.

Following a single oral 300 mg dose of olaparib (tablet formulation) 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 (tablet formulation) 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

Capsule content

Lauroyl macrogol-32 glycerides

Capsule shell

Hypromellose

Gellan gum

Titanium dioxide

Potassium acetate

Printing ink

Shellac

Iron oxide black

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C - 8°C). Do not freeze. Any capsules that have been frozen must be discarded.

LYNPARZA capsules can be stored for up to 3 months below 30°C. The capsules must be discarded after this period.

6.5 NATURE AND CONTENTS OF CONTAINER

HDPE plastic bottles with a cold-resistant closure containing 112 capsules.

Pack of 448 capsules (4 bottles of 112 capsules).

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

10 November 2016

10. DATE OF REVISION OF TEXT

4 November 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	MS/AML section updated
4.8	Patient number for safety pool updated. MS/AML and angioedema added.