LYNPARZA™

olaparib

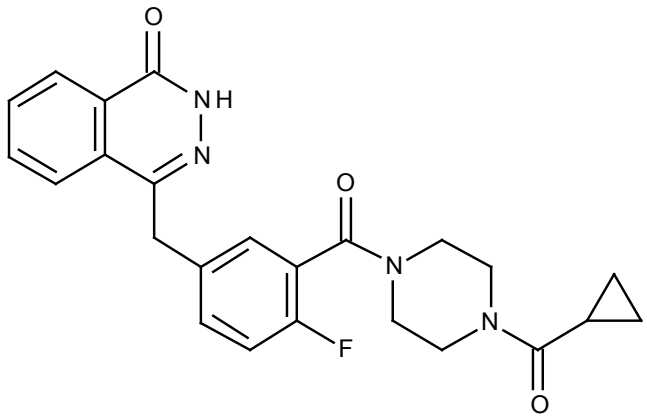
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in LYNPARZA is olaparib, an orally active potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP enzymes).

The chemical name for olaparib is: 4-[[3-[[4-(cyclopropylcarbonyl)-1-piperazinyl]carbonyl]-4-fluorophenyl]methyl]-1(2*H*)-phthalazinone

The chemical structure of olaparib is:



CAS number: 763113-22-0
Molecular formula: $C_{24}H_{23}FN_4O_3$
Molecular weight: 434.46

DESCRIPTION

Olaparib is a white to pale yellow crystalline powder, which is very slightly soluble in aqueous solutions (0.10 – 0.13 mg/mL at 37°C), slightly soluble in ethanol (5.5 mg/mL at 37°C) and has a pKa of 12.07.

LYNPARZA capsules consist of 50 mg olaparib drug substance suspended in the semi-solid lipidic excipient lauroyl macrogol-32 glycerides, within a hypromellose capsule shell which also contains gellan gum, titanium dioxide and potassium acetate. LYNPARZA capsules are white and are marked with “OLAPARIB 50 mg” and the AstraZeneca logo printed in black ink.

PHARMACOLOGY

Pharmacological actions

LYNPARZA is an 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 *BRCA*1 and 2 genes, is effective at repairing these DNA double-strand breaks. In the absence of functional *BRCA*1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability 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 *BRCA*1 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.

Pharmacokinetics

Olaparib displays high inter-patient variability in PK parameters, including Cmax, AUC, Vd 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.

Distribution

The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is ~90%.

Metabolism

In vitro, CYP3A4 was shown to be the enzyme 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 carboxycyclopropyl ring structure and, to a lesser extent the fluorophenyl and the phathalazinone ring systems. 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 hydroxycyclopropyl 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.

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. Majority of the material was excreted as metabolites.

Special populations

Renal impairment

The effect of renal impairment on exposure to LYNPARZA has not been studied.

Hepatic impairment

The effect of hepatic impairment on exposure to LYNPARZA has not been studied.

Race

There are insufficient data to evaluate the potential effect of race on olaparib pharmacokinetics as clinical experience is predominantly in Caucasians (94% of patients included in the population analysis were Caucasian). In the limited data available, there

was no evidence of a marked ethnic difference in the PK of olaparib between Japanese and Caucasian patients.

CLINICAL TRIALS

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, was 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.

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 of statistically significantly improved PFS for LYNPARZA maintenance monotherapy compared with placebo in the overall population (HR 0.35; 95% CI 0.25-0.49; p<0.00001), moreover, preplanned subgroup analysis identified patients with *BRCA*-mutated ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from LYNPARZA maintenance monotherapy.

In *BRCA*-mutated patients (n=136) there was a statistically significant improvement in PFS. 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 vs 4.3). The investigator assessment of PFS was consistent with a blinded independent central radiological review of PFS. There was no statistically significant difference in OS (HR 0.73; 95% CI 0.45- 1.17; p=.0.19; median 34.9 months versus 31.9 months).

In the *gBRCA*-mutated subgroup (n=96) there was a statistically significant improvement in PFS. 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 vs 4.1). There was no statistically significant difference in OS (HR 0.85; 95% CI 0.48- 1.52; p= 0.58; median 32.9 months versus 30.2 months).

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.

A summary of efficacy findings for patients with *BRCA*-mutated and *gBRCA*-mutated PSR ovarian cancer in Study 19 is presented in Table 1 and Figures 1 and 2.

Table 1 Summary of key efficacy findings for patients with *BRCA*-mutated and *gBRCA*-mutated PSR ovarian cancer in Study 19

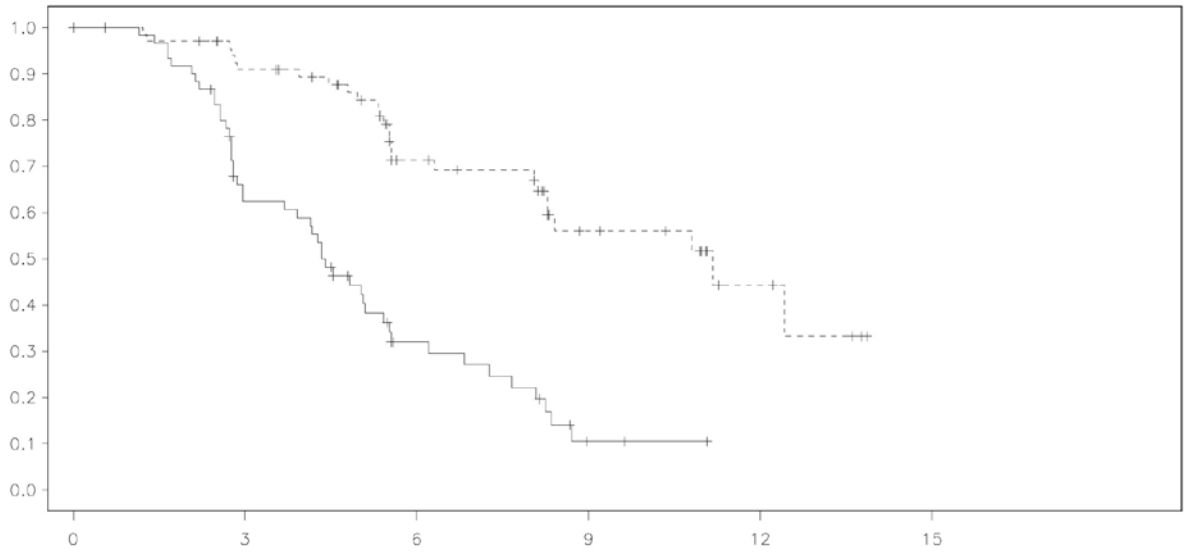
	***BRCA*-mutated**		***gBRCA*-mutated**	
	LYNPARZA 400 mg bid	**Placebo**	**LYNPARZA 400 mg bid**	**Placebo**
	n = 74	n = 62	n = 53	n = 43
PFS				
Number of events: Total number of patients (%)	26:74 (35%)	46:62 (74%)	17:53 (32%)	33:43 (77%)
Median time (months)	11.2	4.3	11.2	4.1
HR (95% CI) [a]	0.18 (95% CI 0.10–0.31)		0.17 (95% CI 0.09-0.31)	
P value (2-sided)	p<0.00001		p<0.00001	
Interim OS (52% maturity)				
Number of events: Total number of patients (%)	37:74 (50%)	34:62 (55%) [b]	27:53 (51%)	22:43 (51%) [b]
Median time (months)	34.9	31.9	32.9	30.2
HR (95% CI) [a]	0.73 (95% CI 0.45–1.17)		0.85 (95% CI 0.48-1.52)	
P value (2-sided)	p=0.19		p=0.58	

[a] HR= Hazard Ratio. A value <1 favours LYNPARZA. The analysis was performed using a Cox proportional hazards model with factors for treatment, time to disease progression on prior platinum therapy, objective response to prior platinum therapy and Jewish decent.

[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 (13/40; 32.5%) received a subsequent PARP inhibitor.

OS overall survival; PFS progression-free survival; CI confidence interval

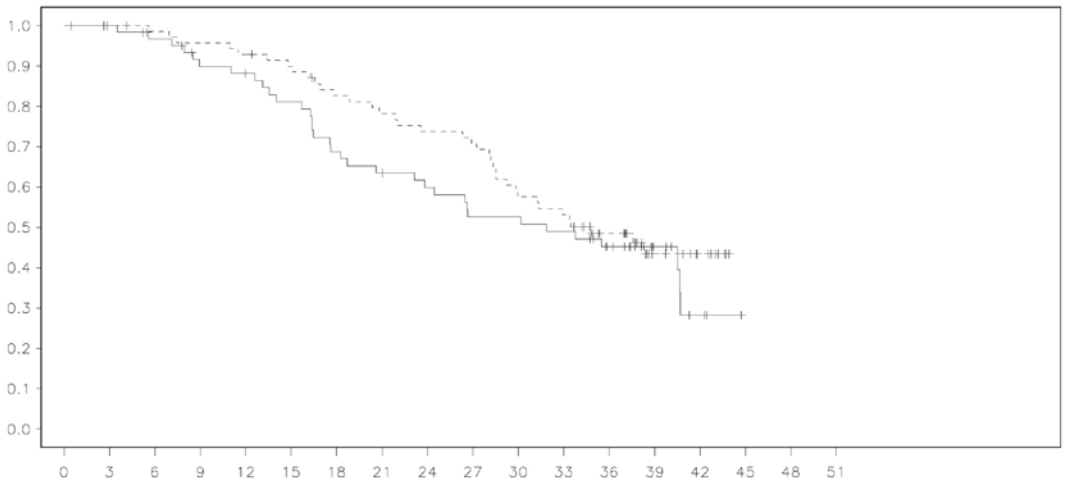
Figure 1 Study 19: Kaplan-Meier plot of PFS in BRCA-mutated patients (53% maturity-investigator assessment)



months	0	3	6	9	12	15
n-LYNPARZA	74	59	34	15	5	0
n-placebo	62	35	13	2	0	0

----- olaparib 400 mg bd twice daily, —— placebo, x-axis=time from randomisation in months, y-axis = PFS (progression-free survival), n-LYNPARZA = number of patients at risk-LYNPARZA, n-placebo = number of patients at risk-placebo

Figure 2 Study 19: Kaplan-Meier plot of OS in *BRCA*-mutated patients (52% maturity)



months	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
n-LYNPARZA	74	71	69	67	65	62	56	53	50	48	39	36	26	12	7	0	0	0
n-placebo	62	62	58	52	50	46	39	36	33	29	29	27	21	10	4	0	0	0

----- olaparib 400 mg bd twice daily, —— placebo, x-axis = time from randomisation in months, y-axis = OS (overall survival), n-LYNPARZA = number of patients at risk-LYNPARZA, n-placebo = number of patients at risk-placebo

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 bd multiple dosing of the olaparib tablet formulation.

Retreatment on relapse

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

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.

CONTRAINDICATIONS

Hypersensitivity to the active substance (olaparib) or to any of the excipients.

PRECAUTIONS

Haematological toxicity

Haematological toxicity occurs commonly in patients treated with olaparib. 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 within normal range or CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

If a patient develops severe 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

Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in a small number of patients (<1%) and the majority of reports have been fatal. The reports were typical of secondary MDS/cancer therapy-related AML. The duration of therapy with olaparib in patients who developed secondary MDS/AML varied from <6 months to >2 years. The majority of reports were in patients with a germline BRCA mutation. All patients had potential contributing factors for the development of MDS/AML, having received extensive previous chemotherapy with platinum agents. Many had also received other DNA damaging agents. If MDS and/or AML are confirmed while on treatment with LYNPARZA, it is recommended that the patient be treated appropriately. If additional anticancer therapy is recommended, LYNPARZA should be discontinued.

Pneumonitis

Pneumonitis has been reported in a small number of patients receiving olaparib, and some reports have been fatal. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or a radiological abnormality occurs, LYNPARZA treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

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.

Use in pregnancy – Category D

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.

LYNPARZA should not be used during pregnancy due to the teratogenic and genotoxic potential of olaparib. No studies have been conducted in pregnant women.

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.

Women of child-bearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of LYNPARZA. 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 INTERACTIONS). A pregnancy test should be performed on all pre-menopausal women prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at one month after receiving the last dose.

Use in lactation

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.

Paediatric use

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

Use in men

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

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with olaparib.

Interactions with other medicinal products

LYNPARZA co-administration with strong CYP3A inducers or inhibitors should be avoided (see INTERACTIONS WITH OTHER MEDICINES).

INTERACTIONS WITH OTHER MEDICINES

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 other anticancer agents.

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. Clinical studies [conducted with a tablet formulation] to evaluate the impact of known CYP3A inhibitors and inducers have shown that co-administration of a potent CYP3A inhibitor increased olaparib C_{max} 1.42-fold (90% CI: 1.33-1.52) and increased mean AUC 2.70-fold (90% CI: 2.44-2.97) and that co-administration of a potent CYP inducer decreased C_{max} by 71% (Treatment ratio: 0.29; 90% CI: 0.24-0.33) and mean AUC by 87% (Treatment ratio: 0.13; 90% CI: 0.11-0.16. It is therefore recommended that known potent inhibitors/inducers of these isozymes are not co-administered with olaparib. These include but are not limited to inducers such as phenytoin, rifampicin, rifabutin, carbamazepine, nevirapine, St John's Wort; and inhibitors such as itraconazole, clarithromycin, boosted protease inhibitors with ritonavir or cobicistat, indinavir, saquinavir, boceprevir, aciprofloxacin, erthyromycin, diltiazem, fluconazole, verapamil) and also grapefruit, star fruit and Seville oranges.

Modest inhibition of CYP3A4 was seen when olaparib was tested at concentrations up to 100 uM and greater inhibition when tested at 500 uM. These findings suggest that olaparib has the potential to cause clinically relevant interactions with other CYP3A4 substrates in the liver or gastrointestinal tract. Olaparib showed time dependent inhibition of CYP3A. The clinical relevance of this is unknown. Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP3A4 being most likely to be induced to a clinically relevant extent.

Olaparib is a substrate for MDR1, but not for BCRP or MRP2. *In vitro* studies suggest it is an inhibitor of MDR1, is a weak inhibitor of BCRP but not an inhibitor of MRP2. It is possible that olaparib may cause clinically relevant drug interactions with substrates of MDR1 such as statins, digoxin, dabigatran and colchicine.

Olaparib has also been shown to be an inhibitor of OATP1B1, OCT2 , OAT3, MATE1 and MATE2K. The clinical relevance of these findings is currently unknown. Olaparib is unlikely to inhibit OCT1, OATP1B3 or OAT1.

Olaparib produced little/no direct inhibition *in vitro* of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1. Olaparib was not a time dependent inhibitor of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2D6 or 2E1.

ADVERSE 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 1 or 2) and generally not requiring treatment discontinuation.

Adverse Drug Reactions during Clinical Trials

The following adverse reactions have been identified in clinical studies with patients receiving LYNPARZA monotherapy. Their frequency is presented in Table 1 Adverse Drug Reactions using CIOMS III frequency classification and then listed by MedDRA SOC and at the preferred term level. Frequencies of occurrence of undesirable effects are defined as: very common (≥1/10); common (³ 1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) including isolated reports. This section includes only data derived from completed monotherapy studies where patient exposure is known.

Table 1 Adverse Drug Reactions during Clinical Trials

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Headache	Very common	Uncommon
	Dysgeusia	Very common	N/A
	Dizziness	Very common	Uncommon
Gastrointestinal disorders	Nausea	Very common	Common
	Vomiting	Very common	Common
	Diarrhoea	Very common	Common
	Dyspepsia	Very common	Not reported
	Stomatitis	Common	Uncommon
	Upper abdominal pain	Common	Uncommon
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Anaemia (decrease in haemoglobin)[a, b]	Very common	Very common

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
	Neutropenia (decrease in absolute neutrophil count) [a, b]	Very common	Common
	Thrombocytopenia (decrease in platelets) [a, b]	Common	Common
	Lymphopenia (decrease in lymphocytes) [a, b]	Very common	Very common
	Mean corpuscular volume elevation [a, c]	Very common	N/A
	Increase in creatinine [a, d]	Very Common	Uncommon

[a] Represents the incidence of laboratory findings, not of reported adverse events.

[b] Decreases were CTCAE grade 2 or greater for haemoglobin, absolute neutrophils, platelets and lymphocytes.

[c] Elevation in mean corpuscular volume from baseline to above the ULN (upper limit of normal). Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

[d] 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. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

DOSAGE AND ADMINISTRATION

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

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

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 ADVERSE EFFECTS) 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 final dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 mg) could be considered.

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 is limited clinical data in patients aged 75 or over.

Renal impairment

The effect of renal impairment on exposure to LYNPARZA has not been studied. LYNPARZA can be administered in patients with mild renal impairment (creatinine clearance >50 ml/min). LYNPARZA is not recommended for use in patients with moderate renal impairment (creatinine clearance <50 ml/min) or severe renal impairment (creatinine clearance <30 ml/min) since there is limited data in such patients and safety and efficacy have not been established.

Hepatic impairment

The effect of hepatic impairment on exposure to LYNPARZA has not been studied. Therefore, LYNPARZA is not recommended for use in patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of normal), as safety and efficacy have not been established.

Women of childbearing potential

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

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 PHARMACOLOGY – Special populations).

Patients with performance status 2 to 4

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

OVERDOSAGE

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

Contact the Poisons Information Centre on 131126 (Australia) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

LYNPARZA 50 mg capsules are white and are marked with “OLAPARIB 50 mg” and the AstraZeneca logo printed in black ink.

LYNPARZA is supplied in cartons containing four HDPE plastic bottles. Each bottle contains 112 capsules.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

7th January 2016

DATE OF MOST RECENT AMENDMENT

N/A