LYNPARZA™
(50 mg hard capsules)

1. NAME OF THE MEDICINAL PRODUCT

'Lynparza'

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg of olaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

'Lynparza' is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

4.2 Posology and method of 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 (either germline or tumour) before 'Lynparza' treatment is initiated. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method (see section 5.1).

There are limited data in patients with somatic BRCA-mutated tumours (see section 5.1).

Genetic counselling for patients with *BRCA* mutations should be performed according to local regulations.

Posology

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

Patients should start treatment with 'Lynparza' no later than 8 weeks after completion of their final dose of the platinum-containing regimen.

It is recommended that treatment be continued until progression of the underlying disease. There are no data on retreatment with 'Lynparza' following subsequent relapse (see section 5.1).

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 reactions

Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (see section 4.8).

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.

Dose adjustments for co-administration with CYP3A inhibitors

Concomitant use of strong and moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong or moderate CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a strong CYP3A inhibitor or 200 mg taken twice daily (equivalent to a total daily dose of 400 mg) with a moderate CYP3A inhibitor (see sections 4.4 and 4.5).

Elderly

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

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Lynparza is 300 mg twice daily (equivalent to a total daily dose of 600 mg) (see section 5.2).

Lynparza can be administered in patients with mild renal impairment (creatinine clearance 51 to 80 ml/min) with no dose adjustment.

Lynparza is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤ 30 ml/min) since there are no data in such patients. Lynparza may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events.

Hepatic impairment
Lynparza can be administered to patients with mild hepatic impairment (Child-Pugh classification A) with no dose adjustment (see section 5.2). Lynparza is not recommended for use in patients with moderate or severe hepatic impairment, as safety and efficacy have not been studied in these patients.

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.

Paediatric population
The safety and efficacy of 'Lynparza' in children and adolescents has not been established. No data are available.

Method of administration
'Lynparza' is for oral use.

Due to the effect of food on olaparib absorption, patients should take 'Lynparza' at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding during treatment and 1 month after the last dose (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity

Haematological toxicity has been reported in patients treated with olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropaenia, thrombocytopaenia and lymphopaenia. Patients should not start treatment with 'Lynparza' until they have recovered from haematological toxicity caused by previous anticancer 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 who received 'Lynparza' alone or in combination with other anti-cancer drugs; the majority of cases have been fatal. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >2 years. The cases were typical of secondary MDS/cancer therapy-related AML. All patients had potential contributing factors for the development of MDS/AML; the majority of cases were in g*BRCA* mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia. All had received previous platinum- containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. 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 and not given in combination with other anticancer therapy.

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.

Embryofoetal toxicity

Based on its mechanism of action (PARP inhibition), olaparib 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.

Pregnancy/contraception

'Lynparza' should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of 'Lynparza' (see section 4.6).

Interactions

Olaparib co-administration 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 olaparib should be reduced (see sections 4.2 and 4.5).

Olaparib co-administration with strong or moderate CYP3A inducers is not recommended (see section 4.5). In the event that a patient already receiving olaparib requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced (see section 4.5).In the event that a patient already receiving olaparib requires treatment with a P-gp inhibitor, careful monitoring of olaparib associated adverse events and management of those events via the dose reduction strategy is recommended (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Clinical studies of olaparib in combination with other anticancer medicinal products, 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 medicinal products.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied.

Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.

Pharmacokinetic interactions

Effect of other drugs on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. A clinical study to evaluate the impact of rifampicin, a known CYP3A inducer has shown that coadministration with olaparib decreased olaparib mean Cmax 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). Therefore, known strong inducers of this isozyme (e.g. phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital, and St John's Wort) are not recommended with olaparib, as it is possible that the efficacy of olaparib could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g. efavirenz, rifabutin) on olaparib exposure is not established, therefore the coadministration of olaparib with these drugs is also not recommended (see section 4.4).

A clinical study to evaluate the impact of itraconazole, a known CYP3A inhibitor has shown that co-administration with olaparib increased mean olaparib Cmax 1.42-fold (90% CI: 1.33-1.52) and mean AUC 2.70-fold (90% CI: 2.44-2.97). Therefore, known strong (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir) or moderate (e.g. erythromycin, diltiazem, fluconazole, verapamil) inhibitors of this isozyme are not recommended with olaparib (see section 4.4). If the strong or moderate CYP3A inhibitors must be coadministered, the dose of olaparib should be reduced. The recommended olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a strong CYP3A inhibitor or 200 mg taken twice daily (equivalent to a total daily dose of 400 mg) with a moderate CYP3A inhibitor (see sections 4.2 and 4.4). It is also not recommended to consume grapefruit juice while on olaparib therapy.

In vitro olaparib is a substrate for the efflux transporter P-gp and therefore P-gp inhibitors may increase exposure to olaparib (see section 4.4).

Effect of olaparib on other drugs

Olaparib may inhibit CYP3A4 *in vitro* and is predicted to be a mild CYP3A inhibitor *in vivo*. 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 olaparib. Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.

Induction of CYP1A2, 2B6 and 3A4 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib (see also sections 4.4 and 4.6).

In vitro, olaparib inhibits the efflux transporter P-gp (IC50 = 76μM), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of medication concomitantly. *In vitro* olaparib has been shown to be an inhibitor of OATP1B1, OCT1,OCT2 OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine) , OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin) and MATE2K (e.g. metformin). In particular, caution should be exercised if olaparib is administered in combination with any statin.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on 'Lynparza' and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing 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 olaparib. Therefore, an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment (see section 4.5).

Pregnancy

Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofoetal survival in the rat at maternal systemic exposures lower than those in humans at therapeutic doses (see section 5.3). There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib, 'Lynparza' should not be used during pregnancy and in women of childbearing potential not using reliable contraception during therapy and for 1 month after receiving the last dose of 'Lynparza'. (See previous paragraph: "Women of childbearing potential/contraception in females" for

further information about birth control and pregnancy testing.)

Breast-feeding

There are no animal studies on the excretion of olaparib in breast milk. It is unknown whether olaparib/or its metabolites are excreted in human milk. 'Lynparza' is contraindicated during breast-feeding and for 1 month after receiving the last dose, given the pharmacologic property of the product (see section 4.3).

Fertility

There are no clinical data on fertility. In animal studies, no effect on conception was observed but there are adverse effects on embryofoetal survival (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, anaemia, neutropaenia, lymphopaenia, mean corpuscular volume elevation, and increase in creatinine.

Tabulated list of adverse reactions

The following adverse reactions have been identified in clinical studies with patients receiving 'Lynparza' monotherapy. Their frequency is presented using CIOMS III frequency classification and then listed by MedDRA System Organ Class (SOC) and at the preferred term level. Frequencies of occurrence of undesirable effects 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); very rare (<1/10,000). This section includes only data derived from completed studies where patient exposure is known.

Table 1: Tabulated list of adverse reactions

	Adverse Reactions

MedDRA System Organ Class	Frequency of All CTCAE grades	Frequency of CTCAE grade 3 and above
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Headache, Dizziness, Dysgeusia,	**Uncommon** Dizziness, Headache
Gastrointestinal disorders	**Very common** Nausea, Vomiting, Diarrhoea, Dyspepsia **Common** Upper abdominal pain, Stomatitis	**Common** Nausea, Vomiting, Diarrhoea **Uncommon** Upper abdominal pain, Stomatitis
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Very common** Anaemia (decrease in haemoglobin)[b,c], Neutropaenia (decrease in absolute neutrophil count)[b,c], Lymphopaenia (decrease in lymphocytes)[b,c], Increase in blood creatinine[b,e], Mean corpuscular volume elevation[b,d], **Common** Thrombocytopaenia (decrease in platelets)[b,c],	**Very common** Anaemia (decrease in haemoglobin)[b,c], Lymphopaenia (decrease in lymphocytes)[b,c] **Common** Neutropaenia (decrease in absolute neutrophil count)[b,c], Thrombocytopaenia (decrease in platelets)[b,c] **Uncommon** Increase in blood creatinine[b,e]

[a] Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, exfoliative rash and generalised erythema. Hypersensitivity includes PTs of hypersensitivity and drug hypersensitivity. Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative. Represents the incidence of laboratory findings, not of reported

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

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

[d] 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.

[e] Data from a double blind placebo controlled study showed a median increase (in percentage change from baseline) up to 23% remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients were CTCAE grade 0 at baseline, and 10% were CTCAE grade 1 at baseline.

Description of selected adverse reactions

Gastrointestinal toxicities are frequently reported with olaparib therapy and are generally low grade (CTCAE grade 1 or 2) and intermittent and can be managed by dose interruption, dose reduction and/or concomitant medicinal products (e.g. antiemetic therapy). Antiemetic prophylaxis is not required.

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. 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.

Paediatric population

No studies have been conducted in paediatric patients.

Other special populations

Limited safety data are available in elderly (age ≥75 years) and non-Caucasian patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX46

Mechanism of action and pharmacodynamic effects

'Lynparza' 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 vivo* either as a standalone treatment or in combination with established chemotherapies.

PARP 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 'Lynparza' 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.

In *BRCA*-deficient *in vivo* models, olaparib given after platinum treatment resulted in a delay in tumour progression and an increase in overall survival compared to platinum treatment alone.

Detection of *BRCA* mutation

Patients are eligible for 'Lynparza' treatment if they have a confirmed deleterious or suspected deleterious *BRCA* mutation (i.e., a mutation that disrupts normal gene function) in either the germline or the tumour (detected using an appropriately validated test).

Clinical efficacy

The safety and efficacy of olaparib as a maintenance therapy in the treatment of platinum-sensitive relapsed (PSR) high grade serous ovarian, including fallopian tube or primary peritoneal cancer patients, 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 olaparib maintenance treatment taken to

progression with no maintenance treatment in 265 (136 olaparib and 129 placebo) PSR serous ovarian cancer patients who were in response (CR [complete response] or PR [partial response]) confirmed as per RECIST and/or as per CA-125 criteria as defined by Gynecologic Cancer InterGroup (GCIG) (at least a 50% reduction in CA-125 levels from the last pre-treatment sample, confirmed 28 days later) following completion of two or more previous platinum containing chemotherapy. The primary endpoint was PFS (progression-free survival) 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- an approximation of PFS2) were also performed.

Only PSR patients with partially platinum-sensitive disease (platinum-free interval of 6 to 12 months) and patients with platinum-sensitive disease (platinum-free interval of >12 months) who were in response following completion of last 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. Retreatment with olaparib was not permitted following progression on olaparib.

Patients were randomised into the study a median of 40 days after completing their final platinum chemotherapy. They received an average of 3 previous chemotherapy regimens (range 2-11) and 2.6 previous platinum-containing chemotherapies (range 2-8).

Patients in the olaparib group continued to receive treatment longer than those in the placebo group. A total of 54 (39.7%) patients received treatment for >12 months in the olaparib group compared with 14 (10.9%) patients in the placebo group.

The study met its primary objective of statistically significantly improved PFS for olaparib maintenance monotherapy compared with placebo in the overall population (HR 0.35; 95% CI 0.25-0.49; p<0.00001), moreover, pre-planned subgroup analysis by BRCA-mutation status identified patients with *BRCA*-mutated ovarian cancer (n=136, 51.3%) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy.

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 for olaparib treated patients (HR 0.18; 95% CI 0.10-0.31; p<0.00001; median 11.2 months versus 4.3 months). The investigator assessment of PFS was consistent with a blinded independent

central radiological review of PFS. 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 0.22–0.50; 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 8.6 months longer for olaparib treated patients (HR 0.44; 95% CI 0.29-0.67; p=0.00013; median 23.8 months versus 15.2 months. 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). Within the *BRCA*-mutated population the disease control rate at 24 weeks was 57% and 24% for patients in the olaparib and placebo groups, respectively.

No statistically significant differences were observed between olaparib and placebo in patient reported symptoms or HRQoL as measured by improvement and worsening rates in the FACT/NCCN Ovarian Symptom Index (FOSI), Trial Outcome Index (TOI) and Functional Analysis of Cancer Therapy– Ovarian total score (FACT-O total).

The key efficacy findings from Study 19 for *BRCA*-mutated patients are presented in Table 2, and Figures 1 and 2.

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

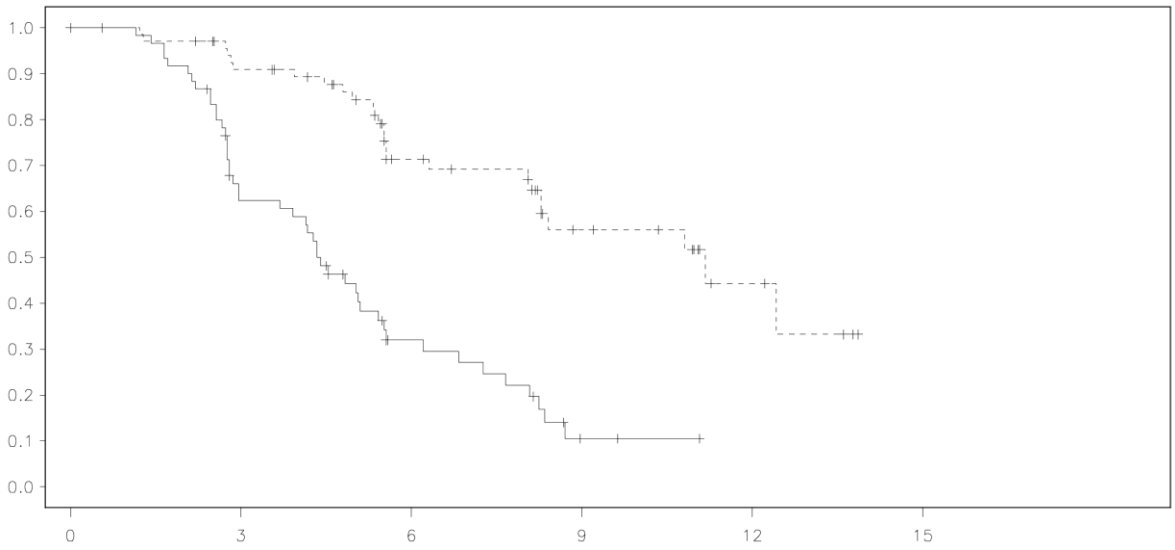
PFS	**N (events/patients) (%)**	**Median PFS (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	26/74 (35%)	11.2	0.18	0.10-0.31	<0.00001
Placebo	46/62 (74%)	4.3			
TSST-an approximation of PFS2	**N**	**Median TSST (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	42/74 (57%)	23.8	0.44	0.29-0.67	0.00013
Placebo	49/62 (79%)	15.2			
Interim OS (52% maturity)	**N**	**Median OS (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	37/74 (50%)	34.9	0.73	0.45-1.17	0.19
Placebo b	34/62 (55%)	31.9			

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

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

[N] Number of events/number of randomised patients; OS Overall survival; PFS Progression-free survival; CI Confidence interval; TSST Time from randomisation to start of second subsequent therapy or death.

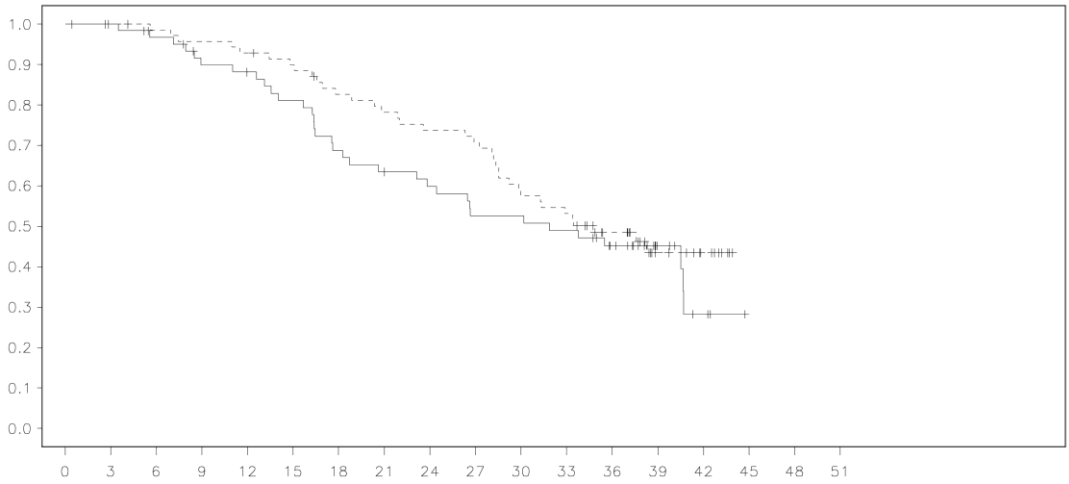
Figure 1: Study 19: Kaplan-Meier plot of PFS in BRCA-mutated patients (53% maturity-investigator assessment)



months	0	3	6	9	12	15
n-olaparib	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-olaparib= number of patients at risk-olaparib, 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-olaparib	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-olaparib= number of patients at risk-olaparib, n-placebo=number of patients at risk-placebo

In Study 19, 18 patients were identified with a somatic tumour *BRCA* mutation (a mutation in the tumour but wildtype in the germline). The limited data for these somatic tumour *BRCA* (*sBRCA*) mutated patients show that fewer patients on olaparib reported progression events or death events compared with placebo (Table 3).

Table 3: Summary of progression-free survival and overall survival: sBRCA mutated population in Study 19

	N events/patients (%)
PFS	
Olaparib 400 mg bd	3/8 (38%)
Placebo	6/10 (60%)
OS	
Olaparib 400 mg bd	4/8 (50%)
Placebo	6/10 (60%)

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with 'Lynparza' in all subsets of the paediatric population, in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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.

Co-administration with food slowed the rate (t_{max} delayed by 2 hours) and marginally increased the extent of absorption of olaparib (AUC increased by approximately 20%). Therefore, it is recommended that patients take 'Lynparza' at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards (see section 4.2).

Distribution

The *in vitro* protein binding of olaparib at plasma concentrations achieved following dosing at 400 mg twice daily is ~82%.

Olaparib is moderately bound to HSA (Humans Serum Albumin) in a non-saturable manner (approximately 55%) and weakly (approximately 35%) bound to AAG (Acid Alpha-1 Glycoprotein).

Biotransformation

In vitro, CYP3A4 was shown to be the enzyme primarily responsible for the metabolism of olaparib (see section 4.5).

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. 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).

In vitro, olaparib produced little/no inhibition of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of the P450 enzymes. *In vitro* data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 substrate and not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination

Following a single dose of ^{14}C-olaparib, ~86% of the dosed radioactivity was recovered within a 7 day collection period, ~44% via the urine and ~42% via the faeces. Majority of the material was excreted as metabolites.

Special populations

Renal impairment

In patients with mild renal impairment (creatinine clearance 51 to 80 ml/min), AUC increased by 24% and Cmax by 15% compared with patients with normal renal function. No Lynparza dose adjustment is required for patients with mild renal impairment.

In patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min), AUC increased by 44% and Cmax by 26% compared with patients with normal renal function. Lynparza dose adjustment is recommended for patients with moderate renal impairment (see section 4.2).

There are no data in patients with severe impairment (creatinine clearance < 30 ml/min).

Hepatic impairment

In patients with mild hepatic impairment (Child-Pugh classification A), AUC increased by 15% and C_{max} by 13% compared with patients with normal hepatic function. No Lynparza dose adjustment is required for patients with mild hepatic impairment (see section 4.2). There are no data in patients with moderate or severe hepatic impairment.

Elderly

There are limited data in patients aged 75 and over. A population analysis of the available data has found no relationship between olaparib plasma concentrations and patient age.

Weight

There are no data in obese (BMI >30 kg/m^2) or underweight (BMI <18 kg/m^2) patients. A population analysis of the available data has found no evidence that patient weight affects

olaparib plasma concentrations.

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.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of olaparib in paediatric patients.

5.3 Preclinical safety data

Genotoxicity

Olaparib showed no mutagenic potential, 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 known 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

In a female fertility study where rats were dosed until implantation, although extended oestrus was observed in some animals, mating performance and pregnancy rate was not affected. However, there was a slight reduction in embryofoetal survival.

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

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, Titanium dioxide (E171), Gellan gum (E418), Potassium acetate

Printing ink: Shellac, Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to expiry date on the outer carton.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE plastic bottle with a child-resistant closure containing 112 hard capsules. Pack of 448 capsules (4 bottles of 112 capsules).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca (Thailand) Limited., Bangkok, Thailand.

8. DATE OF REVISION OF THE TEXT

09 September 2017