ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules

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 AstraZeneca 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 $\leq$ 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 co-administration with olaparib decreased olaparib mean 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). 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 co-administration 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 C_{max} 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 co-administered, 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 inhibits 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 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 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**
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

	Adverse Reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Very common** Anaemia (decrease in haemoglobin)[a, b], Neutropaenia (decrease in absolute neutrophil count)[a, b], Lymphopaenia (decrease in lymphocytes)[a, b], Increase in blood creatinine[a, d], Mean corpuscular volume elevation[a, c] **Common** Thrombocytopaenia (decrease in platelets)[a, b]	**Very common** Anaemia (decrease in haemoglobin)[a, b], Lymphopaenia (decrease in lymphocytes)[a, b] **Common** Neutropaenia (decrease in absolute neutrophil count)[a, b], Thrombocytopaenia (decrease in platelets)[a, b] **Uncommon** Increase in blood creatinine[a, d]

[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 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 listed in Appendix V.

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 until 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

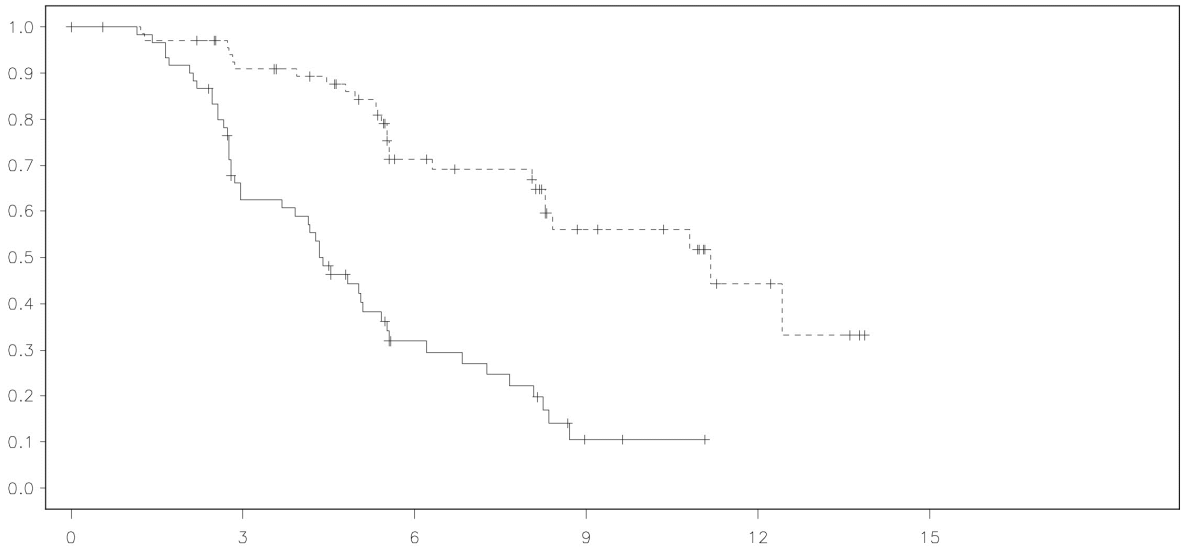
PFS	**N (events/patients) (%)**	**Median PFS (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	26/74 (35%)	11.2	0.18	0.10-0.31	<0.00001
Placebo	46/62 (74%)	4.3			
TSST- an approximation of PFS2	**N**	**Median TSST (months)**	**HR[a]**	**95% CI**	**p-value**
Olaparib 400 mg bd	42/74 (57%)	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.

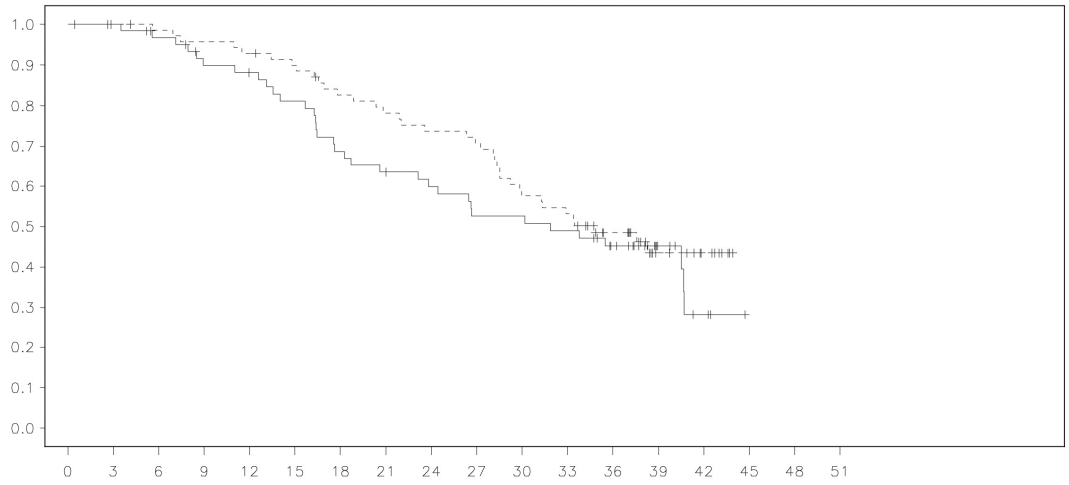
Figure 1 Study 19: Kaplan-Meier plot of PFS in *BRCA*-mutated patients (53% maturity-investigator assessment)



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: s*BRCA* 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 sulfate 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 these P450 enzymes. *In vitro* data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 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 C_{max} 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 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).

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, microphthalmia), 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

18 months.

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 AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca UK Limited
SILK ROAD BUSINESS PARK, MACCLESFIELD, CHESHIRE, SK10 2NA, United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
PAES: In order to further define the long term efficacy of olaparib in patients with platinum sensitive relapsed *BRCA* mutated high grade serous ovarian cancer, the MAH should submit the final Overall Survival (OS) analysis of study D0810C00019, a phase II randomised, double blind, multicentre study. The clinical study report should be submitted by:	June 2017
PAES: In order to further confirm the efficacy of olaparib in patients with platinum sensitive relapsed *BRCA* mutated high grade serous ovarian cancer, the MAH should submit the results of study D0816C00002, a phase III randomised double-blind	

placebo-controlled multicentre study. The clinical study report should be submitted by:	 September 2019
PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed somatic *BRCA* mutated high grade serous ovarian cancer, the MAH should conduct and submit the results of a phase IV, open label, single arm, non-randomised, multicentre study in patients with relapsed platinum sensitive ovarian cancer who are in complete or partial response following platinum based chemotherapy and who carry loss of function germline or somatic *BRCA* mutation(s). The clinical study report should be submitted by:	 September 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
448 capsules (4 bottles of 112 capsules)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE/LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 50 mg hard capsules
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 50 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
112 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/959/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lynparza 50 mg hard capsules
Olaparib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lynparza is and what it is used for

What Lynparza is and how it works

Lynparza hard capsules contain the active substance olaparib. Olaparib is a type of cancer medicine called a PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitor.
In patients with mutations (changes) in certain genes called *BRCA* (breast cancer gene), who are at risk of developing some forms of cancer, PARP inhibitors are able to trigger the death of cancer cells by blocking an enzyme that helps repair DNA.

What Lynparza is used for

Lynparza is used for the treatment of a type of ovarian cancer called "*BRCA*-mutated ovarian cancer". It is used after the cancer has responded to previous treatment with standard platinum-based chemotherapy. A test is used to determine whether you have *BRCA*-mutated cancer.

2. What you need to know before you take Lynparza

Do not take Lynparza:
- if you are allergic to olaparib or any of the other ingredients of this medicine (listed in section 6).

Do not take Lynparza if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist, or nurse before taking Lynparza.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before or during treatment with Lynparza:

- If you have low blood-cell counts on testing. These may be low red blood-cell count (anaemia), low white blood-cell count (neutropaenia), or low blood-platelet count (thrombocytopenia). See section 4 for more information about these side effects. This includes the signs and symptoms you need to look out for (fever or infection, bruising or bleeding). Rarely, these may be a sign of more serious problem with the bone marrow such as 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukaemia' (AML). Your doctor may want to test your bone marrow to check for these problems.

- If you experience any new or worsening symptoms of shortness of breath, coughing, or wheezing. A small number of patients treated with Lynparza reported inflammation of the lungs (pneumonitis). Pneumonitis is a serious condition that can often require hospital treatment.

If any of the above applies to you (or you are not sure), talk to your doctor, pharmacist or nurse.

Tests and checks
Your doctor will check your blood before and during treatment with Lynparza.

You will have a blood test:
- before treatment
- every month for the first year of treatment
- at regular intervals decided by your doctor after the first year of treatment.

If your blood count falls to a low level, it may be necessary to have a blood transfusion (where you are given new blood or blood-based products from a donor).

Other medicines and Lynparza
Tell your doctor, pharmacist, or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Lynparza can affect the way some other medicines work. Also some other medicines can affect the way Lynparza works.

Do not take Lynparza if you are taking any other anticancer medicines. Tell your doctor, pharmacist, or nurse if you are planning on receiving a vaccine or a medicine that suppresses the immune system, as you may need to be closely monitored.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- itraconazole, fluconazole - used for fungal infections
- telithromycin, clarithromycin, erythromycin - used for bacterial infections
- protease inhibitors boosted with ritonavir or cobicistat, boceprevir, telaprevir, nevirapine, efavirenz - used for viral infections, including HIV
- rifampicin, rifapentine, rifabutin - used for bacterial infections, including tuberculosis (TB)
- phenytoin, carbamazepine, phenobarbital - used as a sedative or to treat fits (seizures) and epilepsy
- St John's Wort (*Hypericum perforatum*) - a herbal medicine used mainly for depression
- digoxin, diltiazem, furosemide, verapamil, valsartan – used to treat heart conditions or high blood pressure
- bosentan – used to treat pulmonary artery hypertension
- statins, for example simvastatin, pravastatin – used to lower blood cholesterol levels
- dabigatran – used to thin the blood
- glibenclamide, metformin, repaglinide – used to treat diabetes
- ergot alkaloids – used to treat migraines and headaches

- fentanyl – used to treat cancer pain
- pimozide – used to treat schizophrenia
- quetiapine – used to treat schizophrenia and bipolar disorder
- cisapride – used to treat stomach problems
- colchicine – used to treat gout
- cyclosporine, sirolimus, tacrolimus – used to suppress the immune system
- methotrexate – used to treat cancer, rheumatoid arthritis and psoriasis

Lynparza with drink
Do not drink grapefruit juice throughout the whole period of time you are taking Lynparza. It can affect the way the medicine works.

Pregnancy and breast-feeding
- You should not take Lynparza if you are pregnant or might become pregnant. This is because it may harm an unborn baby.
- You should avoid becoming pregnant while taking this medicine. You should use effective methods of contraception while taking this medicine and for 1 month after receiving the last dose of Lynparza. It is not known whether Lynparza may affect the effectiveness of some oral contraceptives. Please tell your doctor if you are taking an oral contraceptive, as your doctor may recommend the addition of a non-hormonal contraceptive method.
- You should have a pregnancy test before starting Lynparza and at regular times during treatment and 1 month after receiving the last dose of Lynparza. If you become pregnant during this time, you must talk to your doctor straight away.
- It is not known whether Lynparza passes into breast milk. Do not breast-feed if you are taking Lynparza and for one month after receiving the last dose of Lynparza. If you are planning to breast-feed, tell your doctor.

Driving and using machines
Lynparza may influence your ability to drive and use machines. If you feel dizzy, weak, or tired while taking Lynparza, do not drive or use tools or machines.

3. How to take Lynparza

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

How much to take
- The recommended dose is 8 capsules (400 mg) taken by mouth twice a day (a total of 16 capsules each day). It is important that you take the total recommended daily dose and continue to do so as instructed by your doctor, pharmacist, or nurse. Your doctor may prescribe a different dose if you have problems with your kidneys.

How to take
- Take one dose (8 capsules) of Lynparza by mouth with water, once in the morning and once in the evening.
- Take Lynparza at least one hour after eating food. Do not eat preferably for up to 2 hours after taking Lynparza.

If you experience side effects, your doctor may tell you to take Lynparza at a lower dose.

If you take more Lynparza than you should
If you take more Lynparza than your normal dose, contact your doctor or nearest hospital right away.

If you forget to take Lynparza

If you forget to take Lynparza, take your next normal dose at its scheduled time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. It is important that you are aware of what these side effects may be.

Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor straight away if you notice any of the following side effects – you may need urgent medical treatment:

Very common (may affect more than 1 in 10 people):
- fever or infection – these may be signs of a low white blood cell count (neutropaenia or lymphopaenia).
- being short of breath, feeling very tired, having pale skin, or fast heart beat - these may be signs of a low red blood cell count (anaemia).

Common (may affect up to 1 in 10 people):
- bruising or bleeding for longer than usual if you hurt yourself - these may be signs of a low blood platelet count (thrombocytopenia).

Tell your doctor straight away if you notice any of the side effects listed above.

Other side effects include:

Very common
- headache
- feeling dizzy
- loss of appetite
- feeling tired or weak
- feeling sick (nausea)
- being sick (vomiting)
- changes in the way food tastes
- indigestion or heartburn (dyspepsia)
- diarrhoea. If it gets severe, tell your doctor straight away
- increase in blood creatinine levels seen from a laboratory test showing how well your kidneys are working
- blood test showing increase of red blood cell size.

Common
- sore mouth (stomatitis)
- pain in the stomach area under the ribs.

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. Your doctor may prescribe a medicine to treat your symptoms such as nausea, vomiting, diarrhoea, and dyspepsia.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lynparza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lynparza contains
The active substance is olaparib. Each hard capsule contains 50 mg of olaparib.

The other ingredients (excipients) are:
- Capsule content: lauroyl macrogol-32 glycerides.
- Capsule shell: hypromellose, titanium dioxide (E171), gellan gum (E418), potassium acetate.
- Printing ink: shellac, iron oxide black (E172).

What Lynparza looks like and contents of the pack

Lynparza is a white, opaque, hard capsule, marked with “OLAPARIB 50 mg” and the AstraZeneca logo in black ink.

Lynparza is provided in HDPE plastic bottles containing 112 hard capsules. One pack contains 448 capsules (4 bottles of 112 capsules).

Marketing Authorisation Holder

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer

AstraZeneca UK Limited
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.