

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).

Important differences in posology between Lynparza capsules and tablets

Lynparza capsules (50 mg) should not be substituted for Lynparza tablets (100 mg and 150 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.

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 dose reduction is required, then reduction to 100 mg twice daily (equivalent to a total daily dose of 200 mg) is recommended.

Dose adjustments for co-administration with CYP3A inhibitors

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

Special populations

Elderly

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

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 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) as safety and pharmacokinetics have not been studied in these 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 or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see section 5.2). Lynparza is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients.

Non-Caucasian patients

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

Patients with performance status 2 to 4

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

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 Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. 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 \leq CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment (see section 4.8).

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with Lynparza should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Myelodysplastic syndrome/Acute myeloid leukaemia

The incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Lynparza monotherapy, including long-term survival follow-up, was $<1.5\%$ and the majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from < 6 months to > 2 years. All patients had potential contributing factors for the development of MDS/AML; having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA1/2*) mutation carriers. Some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that Lynparza should be discontinued and the patient be treated appropriately.

Pneumonitis

Pneumonitis, including events with a fatal outcome, has been reported in $<1.0\%$ of patients treated with Lynparza in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were

confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

Based on its mechanism of action (PARP inhibition), Lynparza could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that olaparib causes adverse effects on embryofoetal survival and induces major foetal malformations at exposures below those expected at the recommended human dose of 400 mg twice daily.

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

Lynparza 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 Lynparza should be reduced (see sections 4.2 and 4.5).

Lynparza co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza may be substantially reduced (see section 4.5).

4.5 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 myelosuppressive anticancer medicinal products.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these medicinal products are co-administered with Lynparza and patients should be closely monitored.

Pharmacokinetic interactions

Effect of other medicinal products on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib.

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} by 42% (90% CI: 33-52%) and mean AUC by 170% (90% CI: 144-197%). 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 Lynparza (see section 4.4). If strong or moderate CYP3A inhibitors must be co-administered, the dose of Lynparza should be reduced. The recommended Lynparza 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 Lynparza therapy as it is a CYP3A inhibitor.

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% (90% CI: 76-67%) and mean AUC by 87% (90% CI: 89-84%). Therefore, known strong inducers of this isozyme (e.g. phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital, and St John's Wort) are not recommended with Lynparza, as it is possible that the efficacy of Lynparza 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 Lynparza with these medicinal products is also not recommended (see section 4.4).

Effect of olaparib on other medicinal products

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 some 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 ($IC_{50} = 76\mu M$), 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 medicinal product concomitantly.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g. methotrexate, rosuvastatin), 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.

Combination with anastrozole, letrozole and tamoxifen

A clinical study has been performed to assess the combination of olaparib with anastrozole, letrozole or tamoxifen. No significant interaction was observed with anastrozole or letrozole whereas tamoxifen decreased exposure to olaparib by 27%. The clinical relevance of this effect is unknown. Olaparib does not affect the pharmacokinetics of tamoxifen.

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 women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Lynparza (see section 4.4). Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some 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 embryofetal survival (see section 5.3).

4.7 Effects on ability to drive and use machines

Lynparza has moderate influence on the ability to drive and use machines. Patients who take Lynparza may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Lynparza 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 Lynparza monotherapy ($\geq 10\%$) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.

Tabulated list of adverse reactions

The safety profile is based on pooled data from 1,248 patients treated with Lynparza monotherapy in clinical trials in the therapeutic indication at the recommended dose.

The following adverse reactions have been identified in clinical trials with patients receiving Lynparza monotherapy where patient exposure is known. Adverse drug reactions are listed by MedDRA System Organ Class (SOC) and then by MedDRA preferred term level in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data).

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
Blood and lymphatic system disorders	<p>Very common Anaemia^a</p> <p>Common Neutropenia^a, Thrombocytopenia^a, Leukopenia^a</p> <p>Uncommon Lymphopenia</p>	<p>Very common Anaemia^a</p> <p>Common Neutropenia^a, Thrombocytopenia^a, Leukopenia^a</p> <p>Uncommon Lymphopenia</p>
Immune system disorders	<p>Common Rash^a</p> <p>Uncommon Hypersensitivity^a, Dermatitis^a</p>	-
Metabolism and nutrition disorders	<p>Very common Decreased appetite</p>	<p>Uncommon Decreased appetite</p>
Nervous system disorders	<p>Very common Dizziness, Headache, Dysgeusia</p>	<p>Uncommon Dizziness, Headache</p>
Respiratory, thoracic and mediastinal disorders	<p>Very common Cough^a</p>	<p>Uncommon Cough^a</p>
Gastrointestinal disorders	<p>Very common Vomiting, Diarrhoea, Nausea, Dyspepsia</p> <p>Common Stomatitis, Upper abdominal pain</p>	<p>Common Vomiting, Diarrhoea, Nausea</p> <p>Uncommon Stomatitis, Upper abdominal pain</p>
General disorders and administration site conditions	<p>Very common Fatigue (including asthenia)</p>	<p>Common Fatigue (including asthenia)</p>
Investigations	<p>Common Increase in blood creatinine</p> <p>Uncommon Mean corpuscular volume elevation^b</p>	<p>Uncommon Increase in blood creatinine</p>

^a Anaemia includes preferred terms (PTs) of anaemia, haemoglobin decreased, red blood cell count decreased, erythropenia and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia, neutropenic infection and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash

maculo-papular, 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.

- ^b Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.

Description of selected adverse reactions

Haematological toxicity

Anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), however, there were reports of CTCAE grade 3 and higher events. Anaemia was the most common CTCAE grade ≥ 3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE grade ≥ 3 events). Anaemia was managed with dose interruptions and dose reductions (see section 4.2), and where appropriate with blood transfusions. In Study 19, the incidence of anaemia was 22.8% (CTCAE grade ≥ 3 7.4%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 2.9%, 3.7% and 0%, respectively; 10.3% of patients treated with olaparib needed one or more blood transfusions during the treatment. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment (see sections 4.2 and 4.4).

Other laboratory findings

In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of Lynparza treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Lynparza treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

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

Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX46

Mechanism of action and pharmacodynamic effects

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

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this leads to DNA double strand breaks (DSBs) when replication forks meet the PARP-DNA adduct. In normal cells, homologous recombination repair (HRR), which requires functional BRCA1 and 2 genes, is effective at repairing these DNA DSBs. In the absence of functional BRCA1 or 2, DNA DSBs cannot be repaired via HRR. Instead, alternative and error-prone pathways are activated, such as the non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells have a high DNA damage load relative to normal cells.

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, were 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). Platinum free interval was > 12 months in 60% and >6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

Patients in the olaparib group continued to receive treatment longer than those in the placebo group. A total of 32 (23.5%) patients received treatment for ≥ 2 years in the olaparib group compared with 5 (3.9%) patients in the placebo group. A total of 18 (13.2%) patients received treatment for ≥ 5 years in the olaparib group compared with 1 (0.8%) patient in the placebo group.

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

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. Enrolment did not require evidence of *BRCA1/2* mutation (*BRCA* mutation status for some patients was determined retrospectively); 10 patients in the olaparib arm and 10 patients in the placebo arm were defined as having somatic *BRCA1/2* mutation. There was no strategy for multiple testing in place for the sub-group analyses.

In *BRCA*-mutated patients ($n=136$) there was a statistically significant improvement in PFS, TFST, and TSST. The median PFS improvement was 6.9 months over placebo 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. At the final analysis (DCO 9 May 2016), the time from randomisation to start of first subsequent therapy or death (TFST) was 9.4 months longer for olaparib-treated patients (HR 0.33; 95% CI 0.22-0.49;

p<0.00001; median 15.6 months versus 6.2 months). The time from randomisation to start of second subsequent therapy or death (TSST) was 6.1 months longer for olaparib-treated patients (HR 0.43; 95% CI 0.29-0.64; p=0.00003; median 21.4 months versus 15.3 months). For the secondary endpoint of OS, the HR for olaparib versus placebo was 0.62 (95% CI 0.42-0.93; p=0.02140; median 34.9 months versus 30.2 months) (Table 2). In the olaparib-treated group, 28.4% of patients remained on treatment for ≥ 2 years and 14.9% for ≥ 5 years. In the placebo-treated group, 8.1% of patients remained on treatment for ≥ 2 years and 1.6% for ≥ 5 years. 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 (DCO 30 June 2010)	N (events/patients (%))	Median PFS (months)	HR^a	95% CI	p-value* (2-sided)
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 (DCO 09 May 2016)	N	Median TSST (months)	HR^a	95% CI	p-value* (2-sided)
Olaparib 400 mg bd	53/74 (72)	21.4	0.43	0.29-0.64	0.00003
Placebo	56/62 (90)	15.3			
OS (73% maturity) (DCO 09 May 2016)	N	Median OS (months)	HR^a	95% CI	p-value* (2-sided)
Olaparib 400 mg bd	49/74 (66)	34.9	0.62	0.42-0.93	0.02140
Placebo ^b	50/62 (81)	30.2			

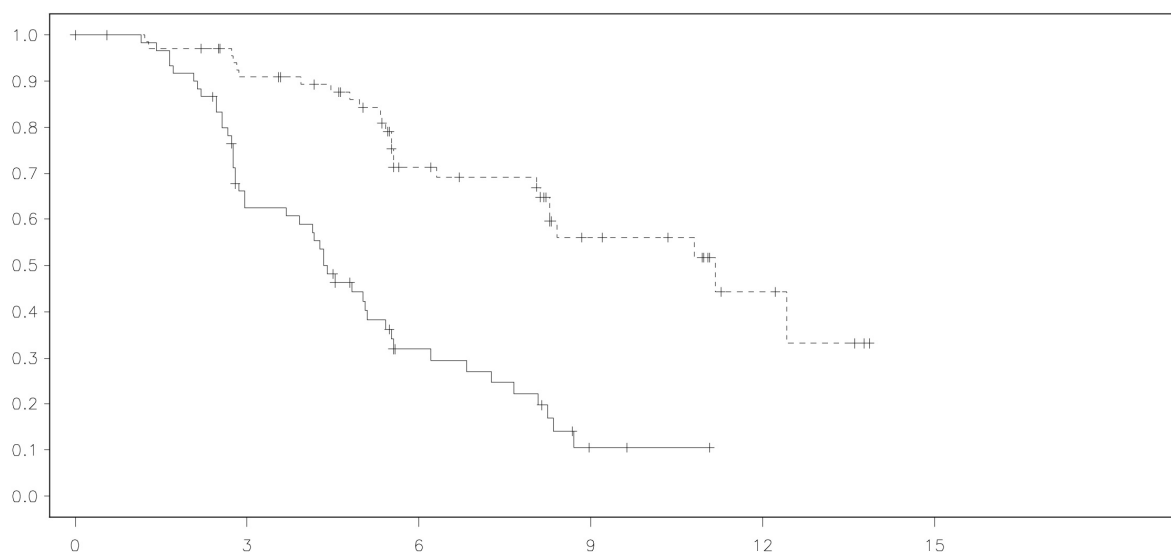
* There was no strategy for multiple testing in place for the sub-group analyses.

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

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

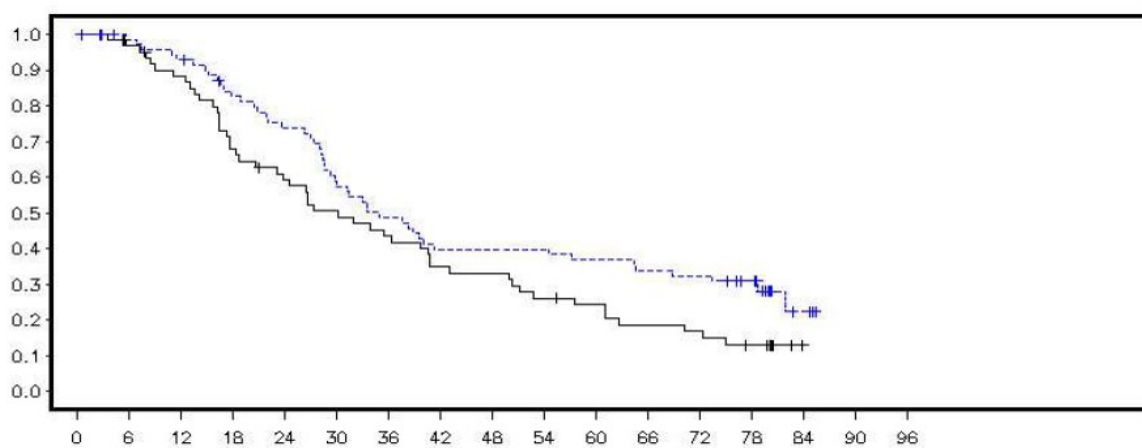
Figure 1 Study 19: Kaplan-Meier plot of PFS in *BRCA*-mutated patients (53% maturity-investigator assessment)



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 (73% maturity)



months	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
n- olaparib	74	69	65	56	50	39	33	27	27	27	25	23	22	16	3	0	0
n- placebo	62	58	52	40	34	29	25	20	19	15	13	10	9	6	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, 20 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	3/10 (30%)
Placebo	8/10 (80%)
OS	
Olaparib 400 mg bd	6/10 (60%)
Placebo	8/10 (80%)

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 is approximately 82% at clinically relevant concentrations of 10 µg/mL.

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

Biotransformation

In vitro, CYP3A4/5 were shown to be the enzymes primarily responsible for the metabolism of olaparib (see section 4.5).

Following oral dosing of ¹⁴C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70%) and was the major component found in both urine and faeces (15% and 6% of the dose respectively). The metabolism of olaparib is extensive. 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 piperazin-3-ol moiety, and two mono-oxygenated metabolites (each ~10%) were the major circulating components, with one of the mono-oxygenated metabolites also being the major metabolite in the excreta (6% and 5% of the urinary and faecal radioactivity respectively).

In vitro, olaparib produced little/no inhibition of UGT2B7, or 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 CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of clinical importance. *In vitro*, olaparib is a substrate of the efflux transporter P-gp, however this is unlikely to be of clinical significance (see section 4.5).

In vitro, data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2, and is not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination

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

Special populations

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

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 or end-stage renal disease (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% and in patients with moderate hepatic impairment (Child-Pugh classification B), AUC increased by 8% and C_{max} decreased by 13% compared with patients with normal hepatic function. No

Lynparza dose adjustment is required for patients with mild or moderate hepatic impairment (see section 4.2). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

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 changes were reversible within 4 weeks of cessation of dosing. In rats, minimal degenerative effects on gastrointestinal tract were also noted. These findings occurred at exposures below those seen clinically. 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>.

▼ 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 100 mg film-coated tablets

Lynparza 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lynparza 100 mg film-coated tablets

Each film-coated tablet contains 100 mg olaparib.

Lynparza 150 mg film-coated tablets

Each film-coated tablet contains 150 mg olaparib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Lynparza 100 mg film-coated tablets

Yellow to dark yellow, oval, bi-convex tablet, debossed with 'OP100' on one side and plain on the other side.

Lynparza 150 mg film-coated tablets

Green to green/grey, oval, bi-convex tablet, debossed with 'OP150' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) 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.

Posology

Lynparza is available as 100 mg and 150 mg tablets.

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

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).

Important differences in posology between Lynparza tablets and capsules

Lynparza tablets (100 mg and 150 mg) should not be substituted for Lynparza capsules (50 mg) on a milligram-to-milligram basis due to differences in the dosing and bioavailability of each formulation. Therefore, the specific dose recommendations for each formulation should be followed.

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

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

Dose adjustments for co-administration with CYP3A inhibitors

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 100 mg (one 100 mg tablet) taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended Lynparza dose reduction is to 150 mg (one 150 mg tablet) taken twice daily (equivalent to a total daily dose of 300 mg) (see sections 4.4 and 4.5).

Special populations

Elderly

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

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Lynparza is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg) (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), as safety and pharmacokinetics have not been studied in these 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 or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment (see section 5.2). Lynparza is not recommended for use in patients with severe hepatic impairment (Child-Pugh classification C), as safety and pharmacokinetics have not been studied in these patients.

Non-Caucasian patients

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

Patients with performance status 2 to 4

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

Paediatric population

The safety and efficacy of Lynparza in children and adolescents have not been established. No data are available.

Method of administration

Lynparza is for oral use.

Lynparza tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Lynparza tablets may be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding during treatment and for 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 Lynparza, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. 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 \leq CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment (see section 4.8).

If a patient develops severe haematological toxicity or blood transfusion dependence, treatment with Lynparza should be interrupted and appropriate haematological testing should be initiated. If the blood parameters remain clinically abnormal after 4 weeks of Lynparza dose interruption, bone marrow analysis and/or blood cytogenetic analysis are recommended.

Myelodysplastic syndrome/Acute myeloid leukaemia

The incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Lynparza monotherapy, including long-term survival follow-up, was $<1.5\%$ and the majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >2 years; data with longer durations of exposure are limited. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA1/2*) mutation carriers. Some of the patients had a history of previous cancer or of

bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that Lynparza should be discontinued and the patient be treated appropriately.

Pneumonitis

Pneumonitis, including events with a fatal outcome, has been reported in <1.0% of patients treated with Lynparza in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, Lynparza treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Lynparza treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

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

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

Lynparza 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 Lynparza should be reduced (see sections 4.2 and 4.5).

Lynparza co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient already receiving Lynparza requires treatment with a strong or moderate CYP3A inducer, the prescriber should be aware that the efficacy of Lynparza may be substantially reduced (see section 4.5).

4.5 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 myelosuppressive anticancer medicinal products.

Combination of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these medicinal products are co-administered with Lynparza and patients should be closely monitored.

Pharmacokinetic interactions

Effect of other medicinal products on olaparib

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib.

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} by 42% (90% CI: 33-52%) and mean AUC by 170% (90% CI: 144-197%). 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 Lynparza (see section 4.4). If strong or moderate CYP3A inhibitors must be co-administered, the dose of Lynparza should be reduced. The recommended Lynparza dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor (see sections 4.2 and 4.4). It is also not recommended to consume grapefruit juice while on Lynparza therapy as it is a CYP3A inhibitor.

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% (90% CI: 76-67%) and mean AUC by 87% (90% CI: 89-84%). Therefore, known strong inducers of this isozyme (e.g. phenytoin, rifampicin, rifapentine, carbamazepine, nevirapine, phenobarbital, and St John's Wort) are not recommended with Lynparza, as it is possible that the efficacy of Lynparza 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 Lynparza with these medicinal products is also not recommended (see section 4.4).

Effect of olaparib on other medicinal products

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 some hormonal contraceptives may be reduced if co-administered with olaparib (see sections 4.4 and 4.6).

In vitro, olaparib inhibits the efflux transporter P-gp ($IC_{50} = 76 \mu M$), 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 medicinal product concomitantly.

In vitro, olaparib has been shown to be an inhibitor of BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. It cannot be excluded that olaparib may increase the exposure to substrates of BCRP (e.g. methotrexate, rosuvastatin), 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.

Combination with anastrozole, letrozole and tamoxifen

A clinical study has been performed to assess the combination of olaparib with anastrozole, letrozole or tamoxifen. No significant interaction was observed with anastrozole or letrozole whereas tamoxifen decreased exposure to olaparib by 27%. The clinical relevance of this effect is unknown. Olaparib does not affect the pharmacokinetics of tamoxifen.

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 women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Lynparza (see section 4.4). Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some 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

Lynparza has moderate influence on the ability to drive and use machines. Patients who take Lynparza may experience fatigue, asthenia or dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Lynparza 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 Lynparza monotherapy ($\geq 10\%$) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, and anaemia.

Tabulated list of adverse reactions

The safety profile is based on pooled data from 1,248 patients treated with Lynparza monotherapy in clinical trials in the therapeutic indication at the recommended dose.

The following adverse reactions have been identified in clinical trials with patients receiving Lynparza monotherapy where patient exposure is known. Adverse drug reactions are listed by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data).

Table 1 Tabulated list of adverse reactions

MedDRA System Organ Class	Adverse reactions	
	Frequency of All CTCAE grades	Frequency of CTCAE grade 3 and above
Blood and lymphatic system disorders	<p>Very common Anaemia^a</p> <p>Common Neutropenia^a, Thrombocytopenia^a, Leukopenia^a</p> <p>Uncommon Lymphopenia</p>	<p>Very common Anaemia^a</p> <p>Common Neutropenia^a, Thrombocytopenia^a, Leukopenia^a</p> <p>Uncommon Lymphopenia</p>
Immune system disorders	<p>Common Rash^a</p> <p>Uncommon Hypersensitivity^a, Dermatitis^a</p>	-
Metabolism and nutrition disorders	<p>Very common Decreased appetite</p>	<p>Uncommon Decreased appetite</p>
Nervous system disorders	<p>Very common Dizziness, Headache, Dysgeusia</p>	<p>Uncommon Dizziness, Headache</p>
Respiratory, thoracic and mediastinal disorders	<p>Very common Cough^a</p>	<p>Uncommon Cough^a</p>
Gastrointestinal disorders	<p>Very common Vomiting, Diarrhoea, Nausea, Dyspepsia</p> <p>Common Stomatitis, Upper abdominal pain</p>	<p>Common Vomiting, Diarrhoea, Nausea</p> <p>Uncommon Stomatitis, Upper abdominal pain</p>
General disorders and administration site conditions	<p>Very common Fatigue (including asthenia)</p>	<p>Common Fatigue (including asthenia)</p>
Investigations	<p>Common Increase in blood creatinine</p> <p>Uncommon Mean corpuscular volume elevation^b</p>	<p>Uncommon Increase in blood creatinine</p>

^a Anaemia includes preferred terms (PTs) of anaemia, haemoglobin decreased, red blood cell count decreased, erythropenia and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia, neutropenic infection and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, 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.

- ^b Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.

Description of selected adverse reactions

Haematological toxicity

Anaemia and other haematological toxicities were generally low grade (CTCAE grade 1 or 2), however, there were reports of CTCAE grade 3 and higher events. Anaemia was the most common CTCAE grade ≥ 3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE grade ≥ 3 events). Anaemia was managed with dose interruptions and dose reductions (see section 4.2), and where appropriate with blood transfusions. In SOLO2, the incidence of anaemia adverse reactions was 43.6% (CTCAE grade ≥ 3 19.5%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16.9%, 8.2% and 3.1%, respectively; 17.9% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the ULN was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment (see sections 4.2 and 4.4).

Other laboratory findings

In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae. 90% of patients had creatinine values of CTCAE grade 0 at baseline and 10% were CTCAE grade 1 at baseline.

Nausea and vomiting

Nausea was generally reported very early, with first onset within the first month of Lynparza treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Lynparza treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

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 limited experience of overdose with olaparib. No unexpected adverse reactions were reported in a small number of patients who took a daily dose of up to 900 mg of olaparib tablets over two days. Symptoms of overdose are not established and there is no specific treatment in the event of Lynparza overdose. In the event of an overdose, physicians should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX46

Mechanism of action and pharmacodynamic effects

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

PARPs are required for the efficient repair of DNA single strand breaks and an important aspect of PARP-induced repair requires that after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells this also leads to the formation of DNA double-strand breaks (DSBs) when replication forks meet the PARP-DNA adducts. In normal cells, homologous recombination repair (HRR) pathway is effective at repairing these DNA DSBs. In cancers that lack functional components of HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively. Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to increased genomic instability. After a number of rounds of replication, genomic instability can reach insupportable levels and result in cancer cell death, as cancer cells already have a high DNA damage load relative to normal cells. In the absence of *BRCA1* or *BRCA2* mutations, HRR pathway may be compromised by other mechanisms, although the causative aberrancy and penetrance are not fully elucidated. Absence of fully functional HRR pathway is one of the key determinants of platinum sensitivity in ovarian and other cancers.

In *BRCA1/2*-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 that correlated with the period of olaparib maintenance treatment.

Detection of *BRCA1/2* mutation

If *BRCA1/2* mutation status is determined, it should be conducted by an experienced laboratory using a validated test method.

Genetic counselling for patients tested for mutations in breast cancer susceptibility genes 1/2 (*BRCA1/2*) should be performed according to local regulations.

Clinical efficacy and safety
SOLO2 study (D0816C00002)

The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until progression with placebo treatment in 295 patients with high-grade serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR [complete response] or PR [partial response]) following completion of platinum-containing chemotherapy.

Patients who have received two or more platinum-containing regimens and whose disease had recurred > 6 months after completion of penultimate platinum-based chemotherapy were enrolled. Patients could not have received prior olaparib or other PARP inhibitor treatment. Patients could have received prior bevacizumab, except in the regimen immediately prior to randomisation.

All patients had evidence of germline *BRCA1/2* mutation (*gBRCA1/2m*) at baseline. Patients with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRCA^{Analysis}® test or from testing a tumour sample using a local test. Large rearrangements in the *BRCA1/2* genes were detected in 4.7% (14/295) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 56 years in both arms. Ovarian cancer was the primary tumour in > 80% of the patients. The most common histological type was serous (> 90%), endometrioid histology was reported in 6% of the patients. In the olaparib arm 55% of the patients had only 2 prior lines of treatment with 45% receiving 3 or more prior lines of treatment. In the placebo arm 61% of patients had received only 2 prior lines with 39% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (81%). Platinum free interval was > 12 months in 60% and > 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 47% and partial in 53% of the patients. In the olaparib and placebo arms, 17% and 20% of patients had prior bevacizumab, respectively.

The primary endpoint was progression free survival (PFS) determined by investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2); OS (overall survival), time from randomisation to discontinuation of treatment or death (TDT), time from randomisation to first subsequent anti-cancer therapy or death (TFST), time from randomisation to start of second subsequent anti-cancer therapy or death (TSST); and health related quality of life (HRQoL).

The study met its primary objective demonstrating a statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a hazard ratio (HR) of 0.30 (95% CI 0.22-0.41; p<0.0001; median 19.1 months olaparib vs 5.5 months placebo). The investigator assessment of PFS was supported with a blinded independent central radiological review of PFS (HR 0.25; 95% CI 0.18-0.35; p<0.0001; median 30.2 months for olaparib and 5.5 months placebo). At 2 years, 43% olaparib-treated patients remained progression free compared with only 15% placebo-treated patients.

A summary of the primary objective outcome for patients with *gBRCA1/2m* PSR ovarian cancer in SOLO2 is presented in Table 2 and Figure 1.

Table 2 Summary of primary objective outcome for patients with *gBRCA1/2m* PSR ovarian cancer in SOLO2

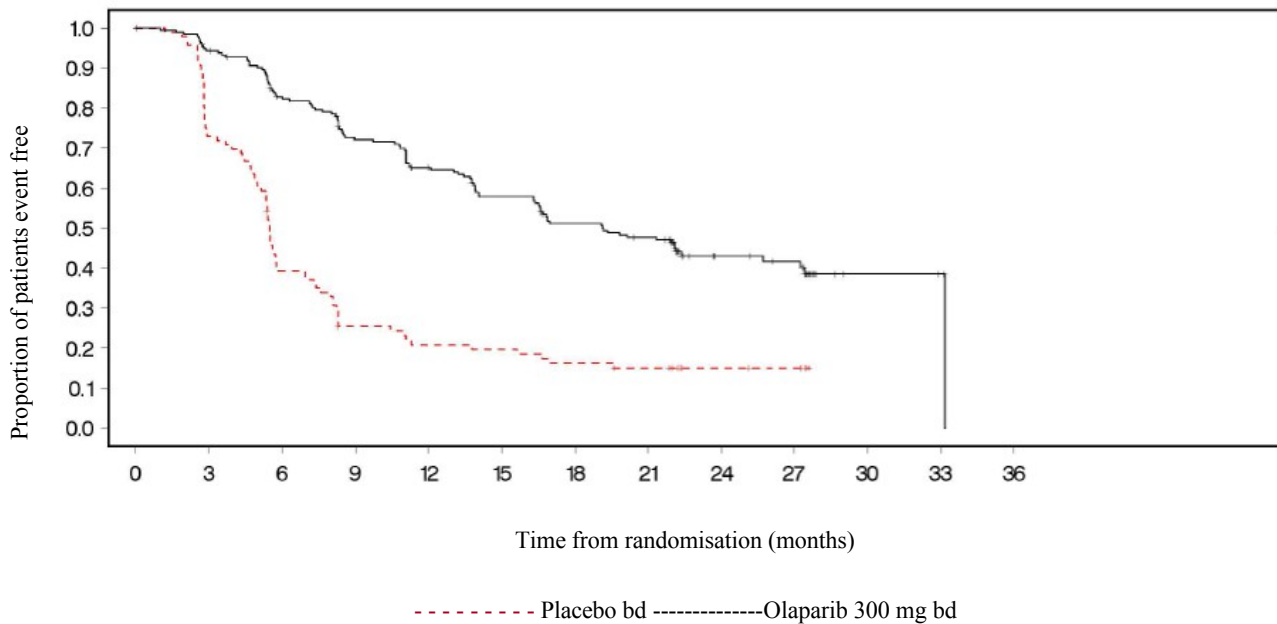
	Olaparib 300 mg tablet bd	Placebo
PFS (63% maturity)		
Number of events: Total number of patients (%)	107:196 (55)	80:99 (81)

	Olaparib 300 mg tablet bd	Placebo
Median time (months) (95% CI)	19.1 (16.3-25.7)	5.5 (5.2-5.8)
HR (95% CI) ^a	0.30 (0.22-0.41)	
P value (2-sided)	p<0.0001	

^a HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy.

bd Twice daily; PFS progression-free survival; CI confidence interval;

Figure 1 SOLO2: Kaplan-Meier plot of PFS in patients with *gBRCA1/2m* PSR ovarian cancer (63% maturity - investigator assessment)



Number of patients at risk:

196	182	156	134	118	104	89	82	32	29	3	2	0	Olaparib 300 mg bd
99	70	37	22	18	17	14	12	7	6	0	0	0	Placebo bd

bd Twice daily; PFS Progression free survival

The secondary endpoints TFST and PFS2 demonstrated a persistent and statistically significant improvement for olaparib compared with placebo (Table 3).

Table 3 Summary of key secondary objective outcomes for patients with *gBRCA1/2m* PSR ovarian cancer in SOLO2

	Olaparib 300 mg tablet bd	Placebo
TFST (58% maturity)		
Number of events: Total number of patients (%)	92:196 (47)	79:99 (80)
Median time (months) (95% CI)	27.9 (22.6-NR)	7.1 (6.3-8.3)
HR (95% CI) ^a	0.28 (0.21-0.38)	
P value* (2-sided)	p<0.0001	
PFS2 (40% maturity)		
Number of events: Total number of patients (%)	70:196 (36)	49:99 (50)
Median time (months) (95% CI)	NR (24.1-NR)	18.4 (15.4-22.8)
HR (95% CI) ^a	0.50 (0.34-0.72)	
P value (2-sided)	p=0.0002	

* Not controlled for multiplicity

^a HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a log-rank test stratified by response to previous platinum chemotherapy (CR or PR), and time to disease progression (>6-12 months and >12 months) in the penultimate platinum-based chemotherapy.

bd Twice daily; NR not reached; CI confidence interval; PFS2 time from randomisation to second progression or death; TFST Time from randomisation to start of first subsequent therapy or death.

Among the patients entering the trial with measurable disease (target lesions at baseline), an objective response rate of 41% was achieved in the Lynparza arm versus 17% on placebo. Of patients treated with Lynparza, who entered the study with evidence of disease (target or non-target lesions at baseline), 15.0% experienced complete response compared with 9.1% of patients on placebo.

At the time of the analysis of PFS the median duration of treatment was 19.4 months for olaparib and 5.6 months for placebo. The majority of patients remained on the 300 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 45.1%, 25.1% and 10.8%, respectively. Dose interruptions occurred most frequently in the first 3 months and dose reductions in the first 3-6 months of treatment. The most frequent adverse reactions leading to dose interruption or dose reduction were anaemia, nausea and vomiting.

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Study 19 (D0810C00019)

The safety and efficacy of olaparib as a maintenance therapy in the treatment of PSR ovarian, including fallopian tube or primary peritoneal cancer patients, following treatment with two or more platinum containing regimens, were studied in a large Phase II randomised, double-blind, placebo-controlled trial (study 19). The study compared the efficacy of Lynparza capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken until progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR high grade serous ovarian cancer patients who were in response (CR or PR) following completion of platinum-containing chemotherapy. The primary endpoint was PFS based on investigator assessment using RECIST 1.0. Secondary efficacy endpoints included OS, disease control rate (DCR) defined as confirmed CR/PR + SD (stable disease), HRQoL and disease related symptoms. Exploratory analyses of TFST and TSST were also performed.

Patients whose disease had recurred >6 months after completion of penultimate platinum-based chemotherapy were enrolled. Enrolment did not require evidence of *BRCA1/2* mutation (*BRCA* mutation status for some patients was determined retrospectively). 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 with *BRCA1/2* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRACAnalysis® test or from testing a tumour sample using a test performed by Foundation Medicine. Large rearrangements in the *BRCA1/2* genes were detected in 7.4% (10/136) of the randomised patients.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 59 years in both arms. Ovarian cancer was the primary tumour in 86% of the patients. In the olaparib arm 44% of the patients had only 2 prior lines of treatment with 56% receiving 3 or more prior lines of treatment. In the placebo arm 49% of patients had received only 2 prior lines with 51% receiving 3 or more prior lines of treatment. Most patients were ECOG performance status 0 (77%). Platinum free interval was > 12 months in 60% and > 6-12 months in 40% of the patients. Response to prior platinum chemotherapy was complete in 45% and partial in 55% of the patients. In the olaparib and placebo arms, 6% and 5% of patients had prior bevacizumab, respectively.

The study met its primary objective demonstrating a statistically significant improvement in PFS for olaparib compared with placebo in the overall population with a HR of 0.35 (95% CI 0.25-0.49; $p < 0.00001$; median 8.4 months olaparib vs 4.8 months placebo). At the final OS analysis (data cut off [DCO] 9 May 2016) at 79% maturity, the hazard ratio comparing olaparib with placebo was 0.73 (95% CI 0.55-0.95; $p = 0.02138$ [did not meet pre-specified significance level of < 0.0095]; median 29.8 months olaparib versus 27.8 months placebo). In the olaparib-treated group, 23.5% ($n = 32/136$) of patients remained on treatment for ≥ 2 years as compared with 3.9% ($n = 5/128$) of the patients on placebo. Although patient numbers were limited, 13.2% ($n = 18/136$) of the patients in the olaparib-treated group remained on treatment for ≥ 5 years as compared with 0.8% ($n = 1/128$) in the placebo group.

Preplanned subgroup analysis identified patients with *BRCA1/2*-mutated ovarian cancer ($n = 136$, 51.3%; including 20 patients identified with a somatic tumour *BRCA1/2* mutation) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. A benefit was also observed in patients with *BRCA1/2* wild-type/variants of uncertain significance (*BRCA1/2 wt/VUS*), although of a lesser magnitude. There was no strategy for multiple testing in place for the sub-group analyses.

A summary of the primary objective outcome for patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in Study 19 is presented in Table 4 and for all patients in Study 19 in Table 4 and Figure 2.

Table 4 Summary of primary objective outcome for all patients and patients with *BRCA1/2*-mutated and *BRCA1/2 wt/VUS* PSR ovarian cancer in study 19

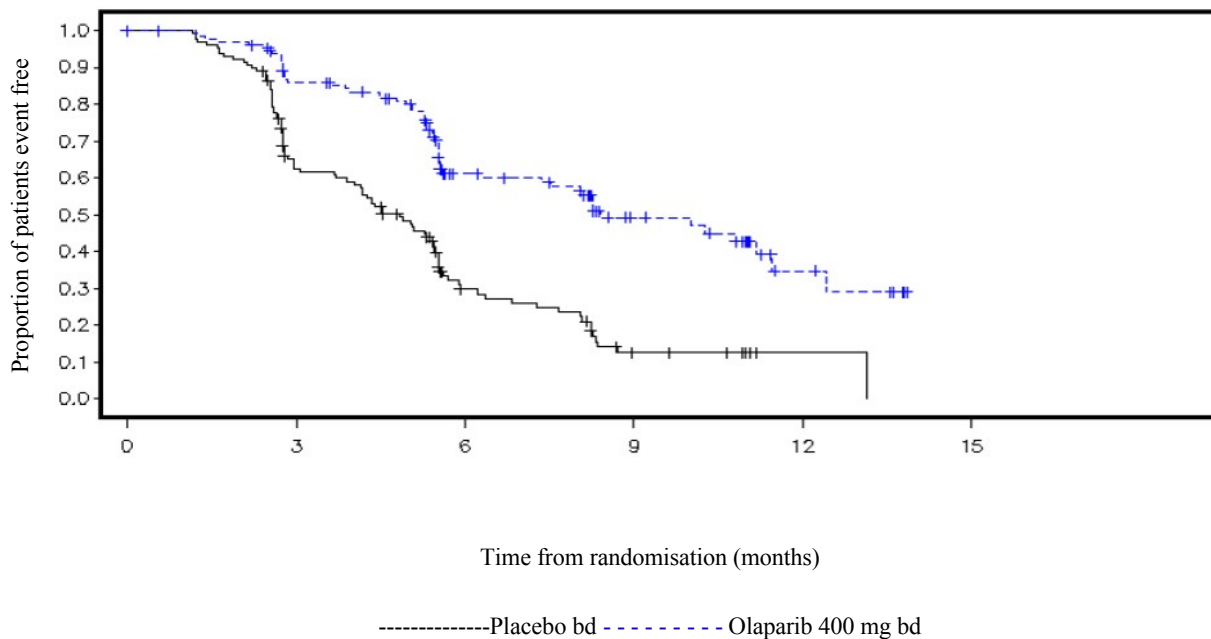
	All patients ^a		<i>BRCA1/2</i> -mutated		<i>BRCA1/2 wt/VUS</i>	
	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo
PFS – DCO 30 June 2010						
Number of events: Total number of patients (%)	60:136 (44)	94:129 (73)	26:74 (35)	46:62 (74)	32:57 (56)	44:61 (72)
Median time (months) (95% CI)	8.4 (7.4-11.5)	4.8 (4.0-5.5)	11.2 (8.3-NR)	4.3 (3.0-5.4)	7.4 (5.5-10.3)	5.5 (3.7-5.6)
HR (95% CI) ^b	0.35 (0.25-0.49)		0.18 (0.10–0.31)		0.54 (0.34-0.85)	
P value (2-sided)	$p < 0.00001$		$p < 0.00001$		$p = 0.00745$	

^a All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt/VUS* and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).

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

bd Twice daily; PFS progression-free survival; DCO data cut off; CI confidence interval; NR not reached.

Figure 2 Study 19: Kaplan-Meier plot of PFS in the FAS (58% maturity - investigator assessment) DCO 30 June 2010



Number of patients at risk:

136	106	53	24	7	0	Olaparib 400 mg bd
129	72	24	7	1	0	Placebo

bd Twice daily; DCO Data cut-off; FAS Full analysis set; PFS progression-free survival

A summary of key secondary objective outcomes for patients with *BRCA1/2*-mutated and *BRCA1/2* wt/VUS PSR ovarian cancer in Study 19 is presented in Table 5 and for all patients in Study 19 in Table 5 and Figure 3.

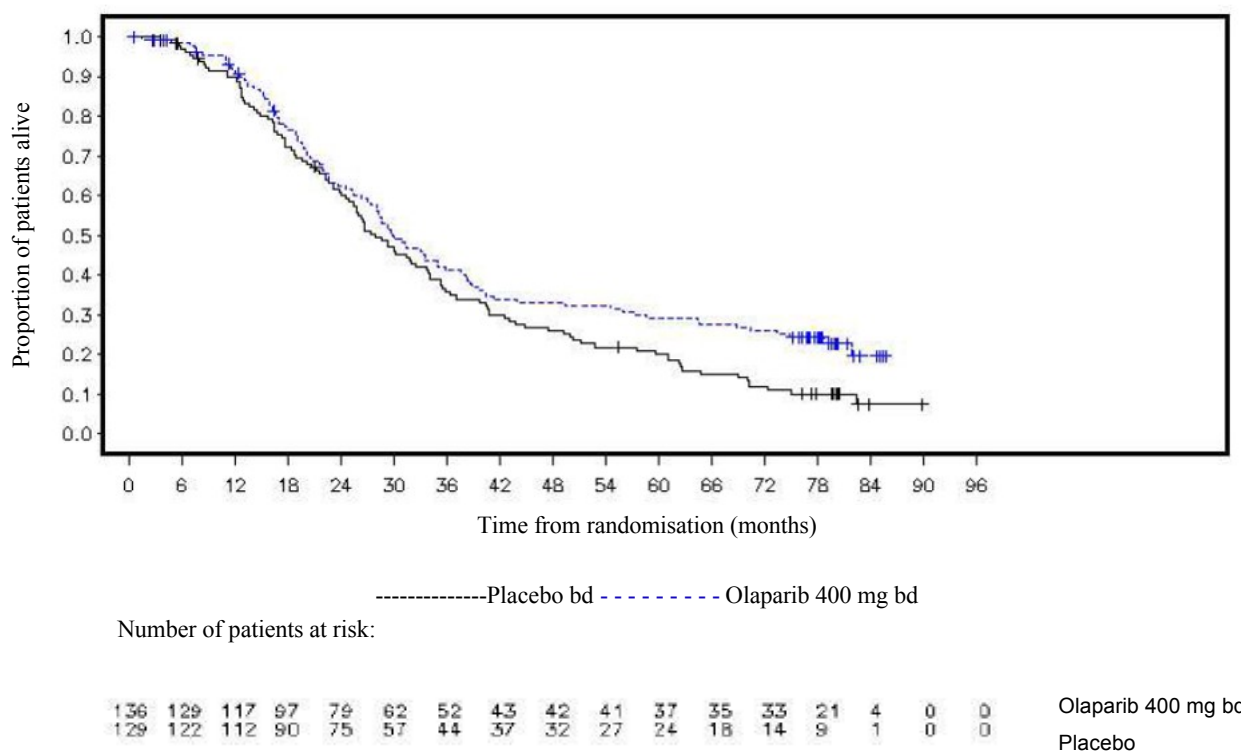
Table 5 Summary of key secondary objective outcomes for all patients and patients with *BRCA1/2*-mutated and *BRCA1/2* wt/VUS PSR ovarian cancer in study 19

	All patients ^a		<i>BRCA1/2</i> -mutated		<i>BRCA1/2</i> wt/VUS	
	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo
OS - DCO 09 May 2016						
Number of events: Total number of patients (%)	98:136 (72)	112:129 (87)	49:74 (66)	50:62 (81) ^c	45:57 (79)	57:61 (93)
Median time (months) (95% CI)	29.8 (26.9-35.7)	27.8 (24.9-33.7)	34.9 (29.2-54.6)	30.2 (23.1-40.7)	24.5 (19.8-35.0)	26.6 (23.1-32.5)
HR (95% CI) ^b	0.73 (0.55-0.95)		0.62 (0.42-0.93)		0.84 (0.57-1.25)	
P value* (2-sided)	p=0.02138		p=0.02140		p=0.39749	
TFST - DCO 09 May 2016						

	All patients ^a		<i>BRCA1/2</i> -mutated		<i>BRCA1/2 wt/VUS</i>	
	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo	Olaparib 400 mg capsule bd	Placebo
Number of events: Total number of patients (%)	106:136 (78)	124:128 (97)	55:74 (74)	59:62 (95)	47:57 (83)	60:61 (98)
Median time (months) (95% CI)	13.3 (11.3-15.7)	6.7 (5.7-8.2)	15.6 (11.9-28.2)	6.2 (5.3-9.2)	12.9 (7.8-15.3)	6.9 (5.7-9.3)
HR (95% CI) ^b	0.39 (0.30-0.52)		0.33 (0.22-0.49)		0.45 (0.30-0.66)	
P value* (2-sided)	p<0.00001		p<0.00001		p=0.00006	

- * There was no strategy for multiple testing in place for the sub-group analyses or for the all patients TFST.
- ^a All patients comprises of the following subgroups: *BRCA1/2*-mutated, *BRCA1/2 wt/VUS* and *BRCA1/2* status unknown (11 patients with status unknown, not shown as a separate subgroup in table).
- ^b HR= Hazard Ratio. A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy.
- ^c Approximately a quarter of placebo-treated patients in the *BRCA*-mutated subgroup (14/62; 22.6%) received a subsequent PARP inhibitor.
- bd Twice daily; OS Overall survival; DCO data cut off; CI confidence interval; TFST time from randomisation to start of first subsequent therapy or death.

Figure 3 Study 19: Kaplan Meier plot of OS in the FAS (79% maturity) DCO 09 May 2016



bd Twice daily; DCO Data cut off; FAS Full analysis set; OS Overall survival

At the time of the analysis of PFS the median duration of treatment was 8 months for olaparib and 4 months for placebo. The majority of patients remained on the 400 mg bd starting dose of olaparib. The incidence of dose interruptions, reductions, discontinuations due to an adverse event was 34.6%, 25.7% and 5.9%, respectively. Dose interruptions and reductions occurred most frequently in the first 3 months of treatment. The most frequent adverse reactions leading to dose interruption or dose

reduction were nausea, anaemia, vomiting, neutropenia and fatigue. The incidence of anaemia adverse reactions was 22.8% (CTCAE grade ≥ 3 7.4%).

Patient-reported outcome (PRO) data indicate no difference for the olaparib-treated patients as compared to placebo as measured by improvement and worsening rates in the Trial Outcome Index (TOI) and Functional Analysis of Cancer Therapy–Ovarian total score (FACT-O total).

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 300 mg tablet dose are characterised by an apparent plasma clearance of ~ 7 L/h, an apparent volume of distribution of ~ 158 L and a terminal half-life of 15 hours. On multiple dosing, an AUC accumulation ratio of 1.8 was observed and PK appeared to be time-dependent to a small extent.

Absorption

Following oral administration of olaparib via the tablet formulation (2 x 150 mg), absorption is rapid with median peak plasma concentrations typically achieved 1.5 hours after dosing.

Co-administration with food slowed the rate (t_{\max} delayed by 2.5 hours and C_{\max} reduced by approximately 21%) but did not significantly affect the extent of absorption of olaparib (AUC increased 8%). Consequently, Lynparza may be taken without regard to food (see section 4.2).

Distribution

The *in vitro* plasma protein binding is approximately 82% at 10 $\mu\text{g/mL}$ which is approximately C_{\max} .

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

Biotransformation

In vitro, CYP3A4/5 were shown to be the enzymes 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 piperazin-3-ol moiety, and two mono-oxygenated metabolites (each $\sim 10\%$) 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 UGT2B7, or 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 CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of

clinical importance. *In vitro*, olaparib is a substrate of the efflux transporter P-gp, however, this is unlikely to be of clinical significance (see section 4.5).

In vitro, data also show that olaparib is not a substrate for OATP1B1, OATP1B3, OCT1, BCRP or MRP2 and is not an inhibitor of OATP1B3, OAT1 or MRP2.

Elimination

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

Special populations

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

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 renal impairment or end-stage renal disease (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% and in patients with moderate hepatic impairment (Child-Pugh classification B), AUC increased by 8% and C_{max} decreased by 13% compared with patients with normal hepatic function. No Lynparza dose adjustment is required for patients with mild or moderate hepatic impairment (see section 4.2). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

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 changes were reversible within 4 weeks of cessation of dosing. In rats, minimal degenerative effects on gastrointestinal tract were also noted. These findings occurred at exposures below those seen clinically. 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

Tablet core

Copovidone
Silica, colloidal anhydrous
Mannitol
Sodium stearyl fumarate

Tablet coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Alu/Alu non-perforated blister containing 8 film-coated tablets.

Pack sizes:

56 film-coated tablets (7 blisters).

Multipack containing 112 (2 packs of 56) film-coated tablets.

Not all pack sizes may be marketed.

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/1/14/959/002
EU/1/14/959/003
EU/1/14/959/004
EU/1/14/959/005

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 confirm the efficacy of olaparib in patients with platinum sensitive relapsed <i>BRCA</i> 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:	June 2020
PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed somatic <i>BRCA</i> mutated high grade serous ovarian cancer, the MAH should conduct and submit the results of a phase IV, open label, single arm, non-	

<p>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 <i>BRCA</i> mutation(s).</p> <p>The clinical study report should be submitted by:</p>	<p>September 2018</p>
<p>PAES: In order to further define the efficacy of olaparib in patients with platinum sensitive relapsed (PSR) non-germline <i>BRCA</i> mutated high grade ovarian cancer in the maintenance setting and investigate predictive biomarkers within this patient group, the MAH should submit the results of study D0816C00020 (OPINION), a phase IIIb single-arm, open-label, multicentre study of maintenance therapy in PSR non-germline <i>BRCA</i> mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.</p> <p>The clinical study report should be submitted by:</p>	<p>June 2021</p>

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

Do not switch to Lynparza tablets unless your doctor tells you

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

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

Do not switch to Lynparza tablets unless your doctor tells you

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.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 film-coated tablets

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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/1/14/959/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 100 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 OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 150 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 film-coated tablets

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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/1/14/959/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 150 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 OUTER PACKAGING

OUTER CARTON MULTIPACK -including the blue box

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack: 112 (2 packs of 56) film-coated tablets

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

EU/1/14/959/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 100 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 OUTER PACKAGING

OUTER CARTON MULTIPACK -including the blue box

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 150 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Multipack: 112 (2 packs of 56) film-coated tablets

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

EU/1/14/959/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 150 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

INNER CARTON – with no blue box

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

56 film-coated tablets

Component of a multipack, not to be sold separately.

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

EU/1/14/959/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INNER CARTON – with no blue box

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 150 mg film-coated tablets
olaparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 150 mg of olaparib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

56 film-coated tablets

Component of a multipack, not to be sold separately.

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

Do not switch to Lynparza capsules unless your doctor tells you

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

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

EU/1/14/959/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lynparza 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 100 mg tablets
olaparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Lynparza 150 mg tablets
olaparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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
2. What you need to know before you take Lynparza
3. How to take Lynparza
4. Possible side effects
5. How to store Lynparza
6. Contents of the pack and other information

1. What Lynparza is and what it is used for

What Lynparza is and how it works

Lynparza contains the active substance olaparib. Olaparib is a type of cancer medicine called a PARP inhibitor (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)
- if you are breast-feeding (see section 2 below for more information).

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 counts for red or white blood cells, or low platelet counts. See section 4 for more information about these side effects, including the signs and symptoms you need to look out for (for example, fever or infection, bruising or bleeding). Rarely, these may be a sign of more serious problems with the bone marrow such as ‘myelodysplastic syndrome’ (MDS) or ‘acute myeloid leukaemia’ (AML).
- 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 you think any of these may apply to you, talk to your doctor, pharmacist or nurse before or during treatment with Lynparza.

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, you may need 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.

Tell your doctor, pharmacist or nurse if you are taking or are planning to take any of the following medicines:

- any other anticancer medicines
- a vaccine or a medicine that suppresses the immune system, as you may need to be closely monitored
- 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
- herbal remedies containing St John’s Wort (*Hypericum perforatum*) - 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, rosuvastatin – 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, quetiapine – used to treat mental health problems
- 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.

Tell your doctor, pharmacist or nurse if you are taking any of the above or any other medicines. The medicines listed here may not be the only ones that could affect Lynparza.

Lynparza with drink

Do not drink grapefruit juice while you are being treated with Lynparza. It can affect the way the medicine works.

Contraception, 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 not become pregnant while taking this medicine. You should use effective methods of contraception while taking this medicine and for 1 month after taking the last dose of Lynparza. It is not known whether Lynparza may affect the effectiveness of some hormonal contraceptives. Please tell your doctor if you are taking a hormonal contraceptive, as your doctor may recommend the addition of a non-hormonal contraceptive method.
- You should have a pregnancy test before starting Lynparza, at regular times during treatment and 1 month after taking 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 1 month after taking 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

Your doctor has prescribed Lynparza **capsules** for you. Please note Lynparza is also available as a 100 mg and 150 mg **tablet**.

- The doses of Lynparza capsules and tablets are not the same. Taking the wrong dose or a tablet instead of a capsule could lead to Lynparza not working properly or to more side effects.

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 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.

How much to take

- Your doctor will tell you how many capsules of Lynparza to take. It is important that you take the total recommended dose each day. Keep doing so for as long as your doctor, pharmacist or nurse tells you to.
- The usual recommended dose is 8 capsules (400 mg) taken by mouth twice a day (a total of 16 capsules each day).

Your doctor may prescribe a different dose if:

- you have problems with your kidneys. You will be asked to take 6 capsules (300 mg) twice a day - a total of 12 capsules each day.
- you are taking certain medicines that may affect Lynparza (see section 2).
- you have certain side effects while you are taking Lynparza (see section 4). Your doctor may lower your dose or stop treatment, either for a short time or permanently.

If you take more Lynparza than you should

If you take more Lynparza than your normal dose, contact your doctor or nearest hospital straight 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 (two doses at the same time) 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.

Tell your doctor straight away if you notice any of the following:**Very common** (may affect more than 1 in 10 people):

- feeling short of breath, feeling very tired, pale skin, or fast heart beat - these may be symptoms of a decrease in the number of red blood cells (anaemia).

Uncommon (may affect up to 1 in 100 people):

- allergic reactions (e.g. hives, difficulty breathing or swallowing, dizziness which are signs and symptoms of hypersensitivity reactions).

Other side effects include:**Very common** (may affect more than 1 in 10 people):

- feeling sick (nausea)
- being sick (vomiting)
- feeling tired or weak
- indigestion or heartburn (dyspepsia)
- loss of appetite
- headache
- changes in taste of foods (dysgeusia)
- feeling dizzy
- cough
- diarrhoea – if it gets severe, tell your doctor straight away.

Common (may affect up to 1 in 10 people):

- rash or itchy rash on swollen, reddened skin (dermatitis)
- sore mouth (stomatitis)
- pain in the stomach area under the ribs (upper abdominal pain).

Common side effects that may show up in blood tests:

- decrease in the number of platelets in blood (thrombocytopenia) - you may notice the following symptoms:

- bruising or bleeding for longer than usual if you hurt yourself
- low white blood cell count (leukopenia, neutropenia or lymphopenia) which may decrease your ability to fight infection and may be associated with fever
- increase in blood creatinine - this test is used to check how your kidneys are working.

Uncommon side effects that may show up in blood tests:

- increase in the size of red blood cells (not associated with any symptoms).

Your doctor will test your blood every month for the first year of treatment and at regular intervals after that. Your doctor will tell you if there are any changes in your blood test that might need treatment.

If you notice any side effects not listed in this leaflet, please contact your doctor straight away.

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).

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Manufacturer

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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>.

Package leaflet: Information for the patient

Lynparza 100 mg film-coated tablets Lynparza 150 mg film-coated tablets 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
2. What you need to know before you take Lynparza
3. How to take Lynparza
4. Possible side effects
5. How to store Lynparza
6. Contents of the pack and other information

1. What Lynparza is and what it is used for

What Lynparza is and how it works

Lynparza contains the active substance olaparib. Olaparib is a type of cancer medicine called a PARP inhibitor (poly [adenosine diphosphate-ribose] polymerase inhibitor).

PARP inhibitors can destroy cancer cells that are not good at repairing DNA damage. These specific cancer cells can be identified by:

- response to platinum chemotherapy, or
- looking for faulty DNA repair genes, such as *BRCA* (BReast CAncer) genes.

What Lynparza is used for

Lynparza is used for the treatment of ovarian cancer that has come back (recurred). It can be used after the cancer has responded to previous treatment with standard platinum-based chemotherapy.

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)
- if you are breast-feeding (see section 2 below for more information).

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 counts for red or white blood cells, or low platelet counts. See section 4 for more information about these side effects, including the signs and symptoms you need to look out for (for example, fever or infection, bruising or bleeding). Rarely, these may be a sign of more serious problems with the bone marrow such as ‘myelodysplastic syndrome’ (MDS) or ‘acute myeloid leukaemia’ (AML).
- 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 you think any of these may apply to you, talk to your doctor, pharmacist or nurse before or during treatment with Lynparza.

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, you may need 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.

Tell your doctor, pharmacist or nurse if you are taking or are planning to take any of the following medicines:

- any other anticancer medicines
- a vaccine or a medicine that suppresses the immune system, as you may need to be closely monitored
- 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
- herbal remedies containing St John’s Wort (*Hypericum perforatum*) -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, rosuvastatin - 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, quetiapine - used to treat mental health problems
- 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.

Tell your doctor, pharmacist or nurse if you are taking any of the above or any other medicines. The medicines listed here may not be the only ones that could affect Lynparza.

Lynparza with drink

Do not drink grapefruit juice while you are being treated with Lynparza. It can affect the way the medicine works.

Contraception, 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 not become pregnant while taking this medicine. You should use effective methods of contraception while taking this medicine and for 1 month after taking the last dose of Lynparza. It is not known whether Lynparza may affect the effectiveness of some hormonal contraceptives. Please tell your doctor if you are taking a hormonal contraceptive, as your doctor may recommend the addition of a non-hormonal contraceptive method.
- You should have a pregnancy test before starting Lynparza, at regular times during treatment and 1 month after taking 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 1 month after taking 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

Your doctor has prescribed Lynparza **film-coated tablets** for you. Please note Lynparza is also available as a 50 mg **capsule**.

- The doses of Lynparza tablets and capsules are not the same.
- Taking the wrong dose or a capsule instead of a tablet could lead to Lynparza not working properly or to more side effects.

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 to take

- Swallow Lynparza tablets whole, with or without food.
- Take Lynparza once in the morning and once in the evening.
- Do not chew, crush, dissolve or divide the tablets as this may affect how quickly the medicine gets into your body.

How much to take

- Your doctor will tell you how many tablets of Lynparza to take. It is important that you take the total recommended dose each day. Keep doing so for as long as your doctor, pharmacist or nurse tells you to.
- The usual recommended dose is 300 mg (2 x 150 mg tablets) twice a day - a total of 4 tablets each day.

Your doctor may prescribe a different dose if:

- you have problems with your kidneys. You will be asked to take 200 mg (2 x 100 mg tablets) twice a day – a total of 4 tablets each day.
- you are taking certain medicines that may affect Lynparza (see section 2).
- you have certain side effects while you are taking Lynparza (see section 4). Your doctor may lower your dose or stop treatment, either for a short time or permanently.

If you take more Lynparza than you should

If you take more Lynparza than your normal dose, contact your doctor or the nearest hospital straight 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 (two doses at the same time) 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.

Tell your doctor straight away if you notice any of the following:

Very common (may affect more than 1 in 10 people):

- feeling short of breath, feeling very tired, pale skin, or fast heart beat – these may be symptoms of a decrease in the number of red blood cells (anaemia).

Uncommon (may affect up to 1 in 100 people):

- allergic reactions (e.g. hives, difficulty breathing or swallowing, dizziness which are signs and symptoms of hypersensitivity reactions).

Other side effects include:

Very common (may affect more than 1 in 10 people):

- feeling sick (nausea)
- being sick (vomiting)
- feeling tired or weak
- indigestion or heartburn (dyspepsia)
- loss of appetite
- headache
- changes in taste of foods (dysgeusia)
- feeling dizzy
- cough
- diarrhoea - if it gets severe, tell your doctor straight away.

Common (may affect up to 1 in 10 people):

- rash or itchy rash on swollen, reddened skin (dermatitis)
- sore mouth (stomatitis)
- pain in the stomach area under the ribs (upper abdominal pain).

Common side effects that may show up in blood tests:

- decrease in the number of platelets in blood (thrombocytopenia) - you may notice the following symptoms:
 - bruising or bleeding for longer than usual if you hurt yourself
- low white blood cell count (leukopenia, neutropenia or lymphopenia) which may decrease your ability to fight infection and may be associated with fever
- increase in blood creatinine - this test is used to check how your kidneys are working.

Uncommon side effects that may show up in blood tests:

- increase in the size of red blood cells (not associated with any symptoms).

Your doctor will test your blood every month for the first year of treatment and at regular intervals after that. Your doctor will tell you if there are any changes in your blood test that might need treatment.

If you notice any side effects not listed in this leaflet, please contact your doctor straight away.

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 blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

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

The other ingredients (excipients) are:

- Tablet core: copovidone, silica colloidal anhydrous, mannitol, sodium stearyl fumarate.

- Tablet coating: hypromellose, macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide black (E172) (150 mg tablets only).

What Lynparza looks like and contents of the pack

Lynparza 100 mg tablets are yellow to dark yellow, oval, bi-convex, film-coated tablets, marked with “OP100” on one side and plain on the other.

Lynparza 150 mg tablets are green to green/grey, oval, bi-convex, film-coated tablets, marked with “OP150” on one side and plain on the other.

Lynparza is supplied in packs containing 56 film-coated tablets (7 blisters of 8 tablets each), or multipacks containing 112 (2 packs of 56) film-coated tablets.

Not all pack sizes may be marketed.

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Other sources of information

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