PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

LYNPARZA® 100 mg, Film-coated tablets

LYNPARZA® 150 mg, Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg film-coated tablet contains 100 mg of olaparib.

Each 150 mg film-coated tablet contains 150 mg of olaparib.

For full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The LYNPARZA 100 mg tablet is a yellow to dark yellow, oval, bi-convex tablet debossed with ‘OP100’ on one side and plain on the reverse side.

The LYNPARZA 150 mg tablet is a green to green/grey, oval, bi-convex tablet debossed with ‘OP150’ on one side and plain on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer

LYNPARZA is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced *BRCA* mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy.
- maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

LYNPARZA in combination with bevacizumab is indicated for the:

- maintenance treatment of adult patients with advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy with bevacizumab.

Breast cancer

LYNPARZA is indicated as monotherapy for the:

- adjuvant treatment of adult patients with *BRCA*-mutated HER2-negative high risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy (see sections 4.2 and 5.1).
- treatment of adult patients with germline *BRCA*-mutated HER2-negative metastatic breast cancer who have previously been treated with chemotherapy. These patients could have received chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

Adenocarcinoma of the pancreas

LYNPARZA is indicated as monotherapy for the:

- maintenance treatment of adult patients with germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on first-line platinum-based chemotherapy.

Prostate cancer

LYNPARZA is indicated as monotherapy for the:

- treatment of adult patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene mutations (germline and/or somatic) who have progressed following a prior new hormonal agent.

LYNPARZA in combination with abiraterone and prednisone or prednisolone is indicated for the:

- treatment of adult patients with metastatic castration-resistant prostate cancer.

4.2 Posology and method of administration

Treatment with LYNPARZA should be initiated and supervised by a medical practitioner experienced in the use of anticancer medicines.

Detection of BRCA and other HRR gene mutations:

Gene mutation status should be determined by an experienced laboratory using a validated test method.

Patient selection

Monotherapy maintenance treatment of advanced BRCA-mutated ovarian cancer:

Patients must have confirmation of a breast cancer susceptibility gene (*BRCA)* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

Adjuvant treatment of BRCA-mutated HER2-negative high risk early breast cancer:

Patients must have confirmation of a *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated.

Metastatic HER2-negative breast cancer:

Patients must have confirmation of a *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

Maintenance following first-line treatment of metastatic gBRCA-mutated metastatic adenocarcinoma of the pancreas:

Patients must have confirmation of a *BRCA* mutation (identified by germline testing) before LYNPARZA treatment is initiated.

Monotherapy treatment of HRR-gene mutated metastatic castration-resistant prostate cancer (mCRPC):

Patients must have confirmation of a homologous recombination repair (HRR) gene mutation (using either tumour DNA from a tissue sample, ctDNA obtained from a plasma sample or germline DNA obtained from a blood or another non-tumour sample) before LYNPARZA treatment is initiated. HRR genetic status should be determined by an experienced laboratory using a validated test method.

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.

Duration of treatment

Monotherapy maintenance treatment of advanced BRCA-mutated ovarian cancer:

Patients can continue treatment for 2 years or until radiological disease progression.

Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating medical practitioner can derive further benefit from continuous treatment, can be treated beyond 2 years.

Platinum-sensitive relapsed ovarian cancer:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Maintenance treatment of advanced ovarian cancer in combination with bevacizumab:
Patients can continue treatment with LYNPARZA for 2 years or until radiological disease progression, unacceptable toxicity. Patients with a complete response (no radiological evidence of disease) at 2 years should stop treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating medical practitioner can derive further benefit from continuous LYNPARZA treatment, can be treated beyond 2 years. When LYNPARZA is used in combination with bevacizumab, refer to the Prescribing Information for bevacizumab for recommended dosing information (see section 5.1).

Adjuvant treatment of BRCA-mutated HER2-negative high risk early breast cancer: It is recommended that patients are treated for a total of 1 year, or until disease recurrence, whichever occurs first. Patients with hormone receptor-positive brtinueast cancer should continue concurrent treatment with endocrine therapy as per local guidelines.

Metastatic HER2-negative breast cancer: It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.
Maintenance following first-line treatment of metastatic adenocarcinoma of the pancreas: It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Monotherapy treatment of HRR-gene mutated metastatic castration-resistant prostate cancer:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

Treatment of metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone:
It is recommended that treatment be continued until progression of the underlying disease (see section 5.1). Please refer to professional information of abiraterone.

Missing dose

If a patient misses a dose of LYNPARZA, the patient should take their next normal dose at its scheduled time.

Dose adjustments

For adverse events

Treatment may be interrupted to manage adverse events 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.

For co-administration with CYP3A inhibitors

Concomitant use of strong or moderate CYP3A inhibitors is not recommended and alternative medicines 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 patient populations

Children or adolescents: LYNPARZA is not indicated for use in paediatric patients, as safety and efficacy of LYNPARZA in children and adolescents have not been established.

Elderly (> 65 years): No adjustment in starting dose is required for elderly patients. There are limited clinical data in patients aged 75 years and over.

Renal impairment: For patients with moderate renal impairment (creatinine clearance 31 – 50 mL/min) the recommended dose of LYNPARZA is 200 mg (two 100 mg tablets) twice daily (equivalent to a total daily dose of 400 mg). LYNPARZA is not recommended for patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤ 30 mL/min), as safety and pharmacokinetics have not been studied in these patients. LYNPARZA can be administered to patients with mild renal impairment (creatinine clearance 51 – 80 mL/min) with no dose adjustment (see section 5.2).

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

Method of administration

For oral use. LYNPARZA tablets should be swallowed whole and not chewed, crushed, dissolved or divided. LYNPARZA tablets can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of LYNPARZA listed in section 6.1.
- Severe renal impairment CrCl < 30 mL/min (see section 4.2).
- Severe hepatic impairment (Child-Pugh class C) (see section 4.2).
- Pregnancy and lactation 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 (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 anti-cancer therapy (haemoglobin, platelet and neutrophil levels should be ≤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 (MDS/AML)

The incidence of MDS/AML in patients treated in clinical trials with LYNPARZA monotherapy, including long-term survival follow up, was <1,5 %, with higher incidence in patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see section 4.8). The majority of events had a fatal outcome. The duration of therapy with LYNPARZA in patients who developed MDS/AML varied from < 6 months to > 4 years. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum medicines. Many had also received other DNA damaging treatments. The majority of reports were in germline *BRCA* mutation (*gBRCAm*) carriers and some of the patients had a history of more than one primary malignancy or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with LYNPARZA, it is recommended that LYNPARZA should be discontinued and the patient be treated appropriately.

Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, have occurred in patients treated with Lynparza and had no consistent clinical pattern. A higher incidence was observed in patients with metastatic castration-resistant prostate cancer, who also received androgen deprivation therapy, compared with other approved indications (see section 4.8). Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Pneumonitis

Pneumonitis has been reported in <1,0 % patients treated with LYNPARZA monotherapy in clinical studies. Reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and

radiotherapy). When LYNPARZA was used in clinical studies in combination with other therapies there have been events with a fatal outcome. If patients present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, LYNPARZA treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, LYNPARZA treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

Based on its mechanism of action (PARP inhibition), LYNPARZA could cause foetal harm when administered to a pregnant woman. Nonclinical studies in rats have shown that LYNPARZA 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.

LYNPARZA should not be taken during pregnancy. If the patient becomes pregnant while taking LYNPARZA, the patient should be apprised of the potential hazard to a foetus.

Pregnancy/contraception

LYNPARZA should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting LYNPARZA treatment, during therapy and for 6 months after receiving the last dose of LYNPARZA (see section 4.6). Two highly effective and complementary forms of contraception are recommended (see section 4.6).

Male patients and their female partners of childbearing potential should be advised that they must use effective contraception during LYNPARZA treatment and for 3 months after receiving the last dose of LYNPARZA (see section 4.6).

Breastfeeding

Breastfeeding mothers should not breastfeed during treatment with LYNPARZA and for one month after receiving the last dose of LYNPARZA (see section 4.6).

Interactions with other medicines

Co-administration of LYNPARZA with strong or moderate CYP3A inhibitors is not recommended (see section 4.5). If a strong or moderate CYP3A inhibitor must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2).

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

4.5 Interaction with other medicines and other forms of interaction

Clinical studies of LYNPARZA in combination with other anticancer medicines, including DNA damaging medicines, indicate a potentiation and prolongation of myelosuppressive toxicity. The recommended LYNPARZA monotherapy dose is not suitable for combination with myelosuppressive anticancer medicines.

Effect of other medicines on LYNPARZA

Strong and moderate CYP3A inhibitors

CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of LYNPARZA. Co-administration of LYNPARZA with a strong CYP3A inhibitor (itraconazole) increased LYNPARZA C_{max} by 42 % and increased AUC by 170 %. Therefore, concomitant use of itraconazole as well as other strong CYP3A inhibitors such as, but not limited to, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir and telaprevir is not recommended with LYNPARZA (see

section 4.4).

Physiologically-based pharmacokinetic (PBPK) modelling has shown that moderate inhibitors will alter the clearance of LYNPARZA and therefore, concomitant use of moderate CYP3A inhibitors such as, but not limited to, ciprofloxacin, erythromycin, diltiazem, fluconazole and verapamil is not recommended with LYNPARZA (see section 4.4).

If strong or moderate CYP3A inhibitors must be co-administered, the dose of LYNPARZA should be reduced (see section 4.2). It is also not recommended to consume grapefruit juice while on LYNPARZA therapy as it is a CYP3A inhibitor.

Strong and moderate CYP3A inducers

Co-administration of LYNPARZA with a strong CYP3A inducer (rifampicin) decreased LYNPARZA C_{max} by 71 % and AUC by 87 %. It is therefore possible that CYP3A inducers could substantially diminish the clinical efficacy of LYNPARZA and as such concomitant use of strong inducers such as, but not limited to, phenytoin, rifabutin, rifampin (rifampicin), rifapentine, carbamazepine, nevirapine, phenobarbitone and St John's Wort (*Hypericum perforatum*) is not recommended with LYNPARZA (see section 4.4).

PBPK modelling has shown that moderate CYP3A inducers will decrease LYNPARZA AUC by approximately 60 % and therefore concomitant use of moderate CYP3A inducers such as, but not limited to bosentan, efavirenz, etravirine, modafinil and nafcillin is not recommended with LYNPARZA. If a moderate CYP3A inducer must be co-administered, the prescriber should be aware of a potential for decreased efficacy of LYNPARZA (see section 4.4).

Effect of LYNPARZA on other medicines

CYP interactions

Both induction and inhibition of CYP3A4 has been shown *in vitro*, however, PBPK simulations

and clinical data suggest that the net effect of LYNPARZA *in vivo* is weak inhibition of CYP3A. Therefore, caution should be exercised when sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, ciclosporin, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine) are combined with LYNPARZA.

Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with LYNPARZA.

Induction of CYP1A2 and 2B6 has been shown *in vitro* with CYP2B6 being most likely to be induced to a clinically relevant extent. Therefore, LYNPARZA upon co-administration may reduce the exposure to substrates of these metabolic enzymes.

Drug transporter interactions

LYNPARZA has also been shown to be an *in vitro* inhibitor of OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. The clinical relevance of these findings is unknown, however, it cannot be excluded that LYNPARZA may increase the exposure to substrates of OATP1B1 (e.g. bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g. metformin), OCT2 (e.g. serum creatinine), OAT3 (e.g. furosemide and methotrexate), MATE1 (e.g. metformin and cisplatin) and MATE2K (e.g. metformin). In particular, caution should be exercised if LYNPARZA is administered in combination with any statin**.**

4.6 Fertility, pregnancy and lactation

Woman of childbearing potential/contraception in males and females

Women of childbearing potential must use two forms of effective contraception before starting LYNPARZA treatment during therapy and for 6 months after receiving the last dose of LYNPARZA (see section 4.4). A pregnancy test should be performed on all women of childbearing potential prior to treatment, and pregnancy tests should be performed at regular intervals during treatment and at 6 months after receiving the last dose.

It is not known whether LYNPARZA or its metabolites are found in seminal fluid. Male patients must use a condom during therapy and for 3 months after receiving the last dose of LYNPARZA when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use effective contraception if they are of childbearing potential (see section 4.4). Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of LYNPARZA.

Pregnancy

LYNPARZA is contraindicated during pregnancy due to the teratogenic and genotoxic potential of LYNPARZA (see section 4.3 and 4.4). Female partners of male patients taking LYNPARZA should also avoid pregnancy. No studies have been conducted in pregnant women (see section 5.3). If a female patient or a female partner of a male patient receiving LYNPARZA becomes pregnant, she should be apprised of the potential hazard to the foetus or potential risk of loss of the pregnancy (see section 4.4).

Breastfeeding

Mothers must not breastfeed their infants while taking LYNPARZA, nor for one month after the last dose (see section 4.3 and 4.4).

Fertility

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

4.7 Effects on ability to drive and use machines

During treatment with LYNPARZA, asthenia, fatigue, and dizziness have been reported and those patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The safety profile is based on pooled data from 4499 patients with solid tumours treated with LYNPARZA monotherapy, 535 patients treated with LYNPARZA in combination with bevacizumab and 469 patients treated with LYNPARZA in combination with abiraterone and prednisone or prednisolone in clinical trials at the recommended dose.

When LYNPARZA is used in combination with bevacizumab for ovarian cancer or in combination with abiraterone and prednisone or prednisolone for prostate cancer, the safety profile is generally consistent with that of the individual therapies.

The following adverse reactions have been identified in completed clinical trials with patients receiving LYNPARZA monotherapy where patient exposure is known. Adverse Drug Reactions are organised by MedDRA System Organ Class (SOC) and then by MedDRA preferred term in Table 1. Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); and very rare (< 1/10 000) including isolated reports.

Table 1 Adverse drug reactions reported in clinical trials with LYNPARZA monotherapy

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (All CTCAE grades)	Frequency of CTCAE grade 3 and above
Neoplasms benign,	Myelodysplastic syndrome/Acute	Uncommon	Uncommon

malignant and unspecified (including cysts and polyps)	myeloid leukaemia[a]		
Blood and lymphatic system disorders	Anaemia[a]	Very common	Very common
	Neutropenia[a]	Very common	Common
	Leukopenia[a]	Very common	Common
	Thrombocytopenia[a]	Common	Common
	Lymphopenia[a]	Common	Common
Immune system disorders	Hypersensitivity[a]	Uncommon	Rare
	Angioedema[*]	Rare	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Dizziness	Very common	Uncommon
	Headache	Very common	Uncommon
	Dysgeusia[a]	Very common	-
Vascular disorders	Thromboembolism (venous)[a]	Common	Common
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	Uncommon
	Dyspnoea[a]	Very common	Common
Gastrointestinal disorders	Vomiting	Very common	Common
	Diarrhoea	Very common	Uncommon
	Nausea	Very common	Common
	Dyspepsia	Very common	Rare
	Stomatitis	Common	Uncommon
	Upper abdominal	Common	Rare

	pain		
Skin and subcutaneous tissue disorders	Rash[a]	Common	Uncommon
	Dermatitis[a]	Uncommon	Rare
	Erythema nodosum	Rare	-
General disorders	Fatigue (including asthenia)	Very common	Common
Investigations	Blood creatinine increased	Common	Rare
	Mean cell volume increased	Uncommon	-

[a] MDS/AML includes preferred terms (PTs) of acute myeloid leukaemia, myelodysplastic syndrome and myeloid leukaemia.

Anaemia includes PTs of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normocytic anaemia and red blood cell count decreased.

Neutropenia includes PTs of febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased.

Leukopenia includes PTs of leukopenia and white blood cell count decreased.

Thrombocytopenia includes PTs of platelet count decreased and thrombocytopenia.

Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia.

Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.

Cough includes PTs of cough and productive cough.

Dyspnoea includes PTs of dyspnoea and dyspnoea exertional.

Dysgeusia includes PTs of dysgeusia and taste disorder.

Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.

Rash includes PTs of erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic.

Dermatitis includes PTs of dermatitis and dermatitis allergic.

Thromboembolism (venous) includes patients of embolism, pulmonary embolism, thrombosis, deep vein thrombosis and venous thrombosis.

*As observed in the post-marketing setting.

Description of selected adverse reactions

Myelodysplastic syndrome/Acute myeloid leukaemia

In clinical studies, across all indications, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and < 1,5 % at any time after starting LYNPARZA, including cases actively solicited during the long term follow up for overall survival.

In patients with *BRCA*m platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and received study treatment until disease progression (SOLO2 study, with LYNPARZA treatment ≥ 2 years in 45 % of patients), the incidence of MDS/AML was 8 % in patients receiving LYNPARZA and 4 % in patients receiving placebo at a follow-up of 5 years. In the LYNPARZA arm, 9 out of 16 MDS/AML cases occurred after discontinuation of LYNPARZA during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the LYNPARZA arm and late onset of MDS/AML. The risk of MDS/AML remains < 1,5 % at 5 year follow up in the first-line setting when LYNPARZA maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years.

Haematological toxicity

Anaemia was the most common CTCAE grade ≥ 3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between LYNPARZA and decreases in haemoglobin has been demonstrated.

In clinical studies with LYNPARZA monotherapy the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 21 %, absolute neutrophils 17 %, platelets 5 %, lymphocytes 26 % and leucocytes 19 % (all % approximate).

The incidence of elevations in mean corpuscular volume from low or normal at baseline to above the upper limit of normal was approximately 51 %. 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 monotherapy the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately 11 %. Data from a double-blind placebo-controlled study showed median increase up to 23 % from baseline remaining consistent over time and returning to baseline after treatment discontinuation.
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.

Paediatric population

No studies have been conducted in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers

are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of overdose are expected to be an exacerbation of the adverse events. There is no specific treatment in the event of LYNPARZA overdose. In the event of an overdose, the medical practitioner should follow general supportive measures and should treat the patient symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XK01

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 or new hormonal agents (NHA)**.**

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 HR-deficient cancer cells, the repair of these DNA

DSBs is impaired. Cancer cells can become HR deficient due to inactivation of genes with a direct or indirect role in HRR, such as *BRCA1/2*, *ATM*, *CDK12* and others. Instead, alternative and error-prone pathways are activated, such as the classical nonhomologous 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 deleterious mutations in key HRR genes, 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.

Pre-clinical studies in prostate cancer models reported a combined anti-tumour effect when PARP inhibitors and next-generation hormonal agents are administered together. PARP is involved in positive co-regulation of androgen receptor (AR) signalling, which leads to enhanced AR target gene suppression when PARP/AR signalling is co-inhibited. Other pre-clinical studies reported that treatment with NHAs inhibit the transcription of some HRR genes, therefore, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms.

Clinical efficacy and safety

Maintenance treatment of *BRCA*-mutated advanced ovarian cancer SOLO1 study

SOLO1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy and safety of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in patients with newly diagnosed advanced (FIGO Stage III-

IV) high-grade serous or endometrioid *BRCA1/2*-mutated (*BRCA1/2m*) ovarian cancer following completion of first – line platinum –based chemotherapy. In this study 391 patients were randomised (2:1 to receive either lynparza 300 mg: 260 patients or placebo (131 patients). Patients were stratified by response to first – line platinum chemotherapy, complete response (CR) or partial response (PR).

Treatment was continued for 2 years or until radiological progression of the underlying disease, or unacceptable toxicity. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease that remained stable (i.e. no evidence of disease progression) could continue to receive LYNPARZA beyond 2 years.

Patients with *BRCA1/2* mutations were identified prospectively either from germline testing in blood via a local test (n=208) or central test (n=181) or from testing a tumour sample using a local test (n=2). The *BRCAm* status of all patients was confirmed where possible using the Myriad Integrated BRAC*Analysis*® test, the Myriad BRACAnalysis CDx® or the Foundation Medicine FoundationOne CDxTM Clinical Trial Assay.
There were 389 patients who were germline *BRCAm* and 2 who were somatic *BRCAm* in SOLO1.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo treatment arms. Median age was 53 years in both arms. Ovarian cancer was the primary tumour in 85 % of the patients. The most common histological type was serous (96 %), endometrioid histology was reported in 2 % of the patients. Most patients were ECOG performance status 0 (78 %). All patients had received first-line platinum-based therapy; response to prior platinum chemotherapy was complete in 82 % and partial in 18 % of the patients. Ninety three percent (93 %) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to the date of randomisation, until objective radiological disease progression.

The study demonstrated a clinically relevant and statistically significant improvement in investigator assessed PFS for olaparib compared to placebo, with a hazard ratio (HR) of 0,30 (95 % CI 0,23 – 0,41; p < 0,0001; the median was not reached for olaparib versus 13,8 months for placebo). Based on Kaplan -Meier estimates, the proportion of patients that were progression free at 12, 24 and 36 months were 88 %, 74 %, and 60 % for olaparib versus 51 %, 35 % and 27 % for placebo; the median follow-up time was 41 months for both the olaparib and placebo treatment arms. The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS (HR 0,28; 95 % CI 0,20 – 0,39; p < 0,0001; median not reached for olaparib vs. 14,1 months for placebo). A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0,50 (95 % CI 0,35 – 0,72; p = 0,0002; median not reached for olaparib vs. 41,9 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies.

At the time of PFS analysis, interim OS data were immature with events in 82/391 (21 %) patients (HR 0,95; 95 % CI 0,60 – 1,53; p = 0,8903; medians not reached). A clinically meaningful and statistically significant improvement in TFST was observed for olaparib treated patients.

There was no decrease in HRQoL from baseline for olaparib-treated patients over the 24-month treatment period and no clinically relevant differences in HRQoL compared with placebo-treated patients as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).

Platinum-sensitive relapsed (PSR) ovarian cancer

The efficacy of LYNPARZA in the maintenance treatment setting in platinum-sensitive relapsed (PSR) ovarian, fallopian tube or primary peritoneal cancer is supported by 2 randomised, double-blind, placebo-controlled trials in patients with PSR and *BRCA*-mutated disease (SOLO2) and in patients with PSR disease (Study 19). In both studies, PSR patients who were in response following completion of platinum-based chemotherapy 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. Patients with *BRCA* mutations were identified either from germline testing in blood via a local test or the Myriad CLIA Integrated BRAC*Analysis*® test or from testing a tumour sample using a local test or a test performed by Foundation Medicine.
In addition, the efficacy of LYNPARZA in the maintenance treatment setting in non-g*BRCA*m PSR ovarian, fallopian tube or primary peritoneal cancer was also assessed in a single-arm, multicentre study (OPINION).

SOLO2 Study in Platinum – Sensitive Relapsed (PSR) patients with a BRCA mutated ovarian [C]cancer

The study compared the efficacy of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken to 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 or PR) following completion of platinum-containing chemotherapy. All patients had evidence of germline *BRCA* mutation (*gBRCAm*) at baseline.

The primary endpoint was PFS determined by investigator assessment using RECIST 1.1. Secondary efficacy endpoints included PFS2; OS, TDT, TFST, TSST; and HRQoL. The study met its primary objective demonstrating a clinically meaningful and statistically significant improvement in investigator assessed PFS for olaparib compared with placebo with a HR of 0,30 (95 % CI 0,22 – 0,41; p < 0,0001; median 19,1 months for olaparib vs. 5,5 months for 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 vs. 5,5 months for placebo). At 2 years, 43 % olaparib-treated patients remained progression-free compared with only 15 % placebo-treated patients. A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0,50 (95 % CI 0,34 – 0,72; p = 0,0002; median not reached for olaparib vs. 18,4 months for placebo) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. At the final analysis of OS (61 % maturity) the HR was 0,74 (95 % CI 0,54 – 1,00; p = 0,0537; median 51,7 months for olaparib vs 38,8 months for placebo) which did not reach statistical significance.
Clinically meaningful and statistically significant improvements in TDT, TFST and TSST were also observed for olaparib-treated patients.

There was no difference between olaparib and placebo treatment groups in HRQoL as assessed by the change from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O) over 12 months (estimated difference – 0,03; 95 % CI: -2,191, 2,2126; p = 0,9765).

Study 19 in PSR patients

The study compared the efficacy of LYNPARZA capsule maintenance treatment (400 mg [8 x 50 mg capsules] twice daily) taken to progression with placebo treatment in 265 (136 olaparib and 129 placebo) PSR 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), HRQoL, and disease related symptoms.

The study met its primary objective demonstrating a statistically significant and clinically relevant improvement in PFS for olaparib compared with placebo with a HR of 0,35 (95 % CI 0,25 – 0,49; p < 0,00001; median 8,4 months for olaparib vs. 4,8 months for placebo). At the final analysis (data cut off [DCO] 9 May 2016) for OS at 79 % maturity, the HR comparing olaparib with placebo was 0,73 (95 % CI 0,55 – 0,95; p = 0,02138 [did not meet pre-specified significance level of < 0,0095]; median 29,8 months for olaparib vs. 27,8 months for placebo). Preplanned subgroup analysis identified patients with *BRCA*m ovarian cancer (n=136, 51,3 %) as the subgroup that derived the greatest clinical benefit from olaparib maintenance monotherapy. There were no multiplicity strategies in place for the sub-group analyses. In *BRCA*m patients the HR for PFS improvement was 0,18 (95 % CI 0,10 – 0,31; p < 0,00001; median 11,2 months for olaparib vs. 4,3 months for placebo). For the secondary endpoint of OS, the HR for olaparib vs. placebo was 0,62 (95 % CI 0,42 – 0,93; p = 0,02140; median 34,9 months for olaparib vs. 30.2 months for placebo). 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 overall population, the DCR at 24 weeks was 53 % and 25 % for patients in the olaparib and placebo groups, respectively and in the *BRCA*m population was 57 % and 24 % for patients in the olaparib and placebo groups, respectively.

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

OPINION study in non-gBRCAm PSR ovarian cancer patients

OPINION was a single arm, multicentre study that investigated olaparib (300 mg [2 x 150 mg tablets] twice daily) as a maintenance treatment in patients with PSR high grade serous or endometrioid ovarian cancer following 2 or more lines of platinum based chemotherapy and who did not have a known deleterious or suspected deleterious g*BRCA* mutation. Patients whose disease was in response (CR or PR) following completion of platinum based chemotherapy were enrolled. A total of 279 patients were enrolled and received olaparib treatment until disease progression or unacceptable toxicity.

The primary endpoint was investigator-assessed PFS (time from the date of the first olaparib dose to the date of objective radiological disease progression according to modified RECIST v1.1 or death by any cause in the absence of progression). Secondary endpoints included OS.

Olaparib when used as maintenance therapy, demonstrated clinical activity in patients with non-g*BRCA*m PSR ovarian cancer with a median investigator-assessed PFS of 9,2 months in the total study population. This was consistent with a sensitivity analysis in which a median investigator-assessed PFS of 9,1 months was observed in the study participants confirmed not to have a deleterious g*BRCA*m. At the time of primary PFS analysis, the OS data were 30 % mature.

First-line maintenance treatment of advanced ovarian cancer

PAOLA-1 was a Phase III randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy of LYNPARZA (300 mg [2 x 150 mg tablets] twice daily) in combination with bevacizumab (15 mg/kg of body weight given once every 3 weeks as an intravenous infusion) compared with placebo plus bevacizumab for the maintenance treatment of newly-diagnosed advanced (FIGO Stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, following first-line platinum-based chemotherapy and

bevacizumab. Treatment with bevacizumab was for a total of up to 15 months/22 cycles, including the period given with chemotherapy and given as maintenance.

The study randomised 806 patients (2:1 randomisation: 537 olaparib/bevacizumab: 269 placebo/bevacizumab) who had no evidence of disease (NED) due to complete surgical resection, or who were in complete response (CR), or partial response (PR) following completion of first-line platinum-containing chemotherapy and bevacizumab. Patients were stratified by first-line treatment outcome (timing and outcome of cytoreductive surgery and response to platinum-based chemotherapy) and t*BRCAm* status, determined by prospective local testing. Patients continued bevacizumab in the maintenance setting and started treatment with LYNPARZA after a minimum of 3 weeks and up to a maximum of 9 weeks following completion of their last dose of chemotherapy. Treatment with LYNPARZA was continued for up to 2 years in the absence of unacceptable toxicity or until progression of the underlying disease was diagnosed. Patients who in the opinion of the treating physician could derive further benefit from continuous treatment could be treated beyond 2 years. Treatment with bevacizumab was for a total of up to 15 months, including the period given with chemotherapy and given as maintenance.

Demographic and baseline characteristics were well balanced between both arms. The median age of patients in both arms was 61 years overall (range 26 to 87). Most patients in both arms were ECOG performance status 0 (70 %). Ovarian cancer was the primary tumour in 86 % of the patients in both arms. The most common histological type was serous (96 %) and endometrioid histology was reported in 2 % of the patients. Most patients were diagnosed in FIGO stage IIIC (63 %). All patients had received first-line platinum-based therapy and bevacizumab. Patients were not restricted by the surgical outcome with 65 % having complete cytoreduction at initial or interval debulking surgery and 35 % having residual macroscopic disease.

The median duration of treatment with LYNPARZA was 17,3 months and 15,6 months for placebo. The median duration of bevacizumab post-randomisation was 11,0 months on the

LYNPARZA arm and 10,4 months on the placebo arm.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to first subsequent anti-cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had RECIST 1.1 tumour assessments at baseline and every 24 weeks (CT/MRI at 12 weeks if clinical or CA 125 progression) for up to 42 months or until objective radiological disease progression.

The study demonstrated a clinically meaningful and statistically significant improvement in investigator assessed PFS for olaparib/bevacizumab compared to placebo/bevacizumab. The investigator assessment of PFS was supported with a BICR of PFS (HR 0,63; 95 % CI 0,51 – 0,77, p < 0,0001 with a median of 26,1 months for olaparib/bevacizumab vs 18,3 months for placebo/bevacizumab).

Final analysis of PFS2 was statistically significant. Although not controlled for multiplicity, there was a clinically meaningful delay in TFST observed for olaparib-treated patients. At the time of final PFS2 analysis, interim OS data were immature (38 %).

Overall, HRQoL remained stable across the 24-month treatment period in patients receiving olaparib or placebo in combination with bevacizumab. There was no clinically meaningful difference in mean change from baseline of the EORTC QLQ-C30 global health status/QoL score for olaparib/bevacizumab-treated patients compared with placebo/bevacizumab-treated patients (estimated difference 0,59; 95 % CI -1,40 – 2,57, p = 0,5626).

***Adjuvant* treatment of *BRCA*-mutated HER2-negative high risk early breast cancer**

OlympiA study in HER2-negative high risk early breast cancer patients with a germline BRCA mutation

OlympiA was a Phase III randomised, double-blind, parallel group, placebo-controlled, multicentre study to assess the efficacy and safety of olaparib (300 mg [2 x 150 mg tablets] twice daily) vs placebo as adjuvant treatment in patients with germline *BRCA1/2* mutations and HER2-negative high risk early breast cancer who had completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Patients were required to have completed at least 6 cycles of neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or both. Prior platinum for previous cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer was allowed. High risk early breast cancer patients were defined as follows:

- patients who received prior neoadjuvant chemotherapy: patients with either triple negative breast cancer (TNBC) or hormone receptor positive breast cancer must have had residual invasive cancer in the breast and/or the resected lymph nodes (non-pathologic complete response) at the time of surgery. Additionally, patients with hormone receptor positive breast cancer must have had a score of ≥ 3 based on pre-treatment clinical and post-treatment pathologic stage (CPS), estrogen receptor (ER) status and histologic grade as shown in Table 2.

Table 2 Early breast cancer stage, receptor status and grade scoring requirements for study enrolment*

Stage/feature		**Points**
Clinical stage (pre-treatment)	I/IIA	0
	IIB/IIIA	1
	IIIB/IIIC	2

Pathologic stage (post-treatment)	0/I	0
	IIA/IIB/IIIA/IIIB	1
	IIIC	2
Receptor status	ER positive	0
	ER negative	1
Nuclear grade	Nuclear grade 1-2	0
	Nuclear grade 3	1

* Total score of ≥ 3 required for patients with hormone receptor positive breast cancer.

- patients who have received prior adjuvant chemotherapy: triple negative breast cancer (TNBC) patients must have had node positive disease or node negative disease with a ≥ 2 cm primary tumor; ER and/or PgR positive, HER2-negative patients must have had ≥ 4 pathologically confirmed positive lymph nodes.

Patients were randomised in a 1:1 ratio to either olaparib (n=921) or placebo (n=915). Randomisation was stratified by hormone receptor status (ER and/or PgR positive/ HER2 negative versus TNBC), by prior neoadjuvant versus adjuvant chemotherapy, and by prior platinum use for breast cancer (yes versus no). Treatment was continued for 1 year, or until disease recurrence, or unacceptable toxicity. Patients with HR positive (ER and/or PgR positive) tumours also received endocrine therapy.

The primary endpoint was invasive disease free survival (IDFS), defined as the time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, contralateral invasive breast cancer, new cancer or death from any cause. Secondary objectives included OS, distant disease free survival [(DDFS, defined as the time from randomisation until evidence of first distant recurrence of breast cancer), the incidence of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian

cancer, new primary fallopian tube cancer and new primary peritoneal cancer], and patient reported outcomes using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires.

Central testing with Myriad BRACAnalysis® or local g*BRCA* testing, if available, was used to establish study eligibility. Patients enrolled based on local g*BRCA* test results provided a sample for retrospective confirmatory testing with BRACAnalysis® (excluding patients enrolled in China). Out of 1836 patients enrolled into OlympiA, 1539 were confirmed as g*BRCAm* by Myriad BRACAnalysis®, either prospectively or retrospectively.

Demographic and baseline characteristics were well balanced between the arms. The median age was 42 years. Sixty-seven percent (67 %) of patients were White, 29 % Asian and 2,6 % Black. Two patients (0,2 %) in the olaparib arm and four patients (0,4 %) in the placebo arm were male. Sixty-one percent (61 %) of patients were pre-menopausal. Eighty-nine percent (89 %) of patients were ECOG performance status 0 and 11 % ECOG PS 1. Eighty-two percent (82 %) of patients had TNBC and 18 % had hormone receptor-positive disease (defined as ER positive and/or PgR positive). Fifty percent (50 %) of patients had received prior neoadjuvant and 50 % received prior adjuvant chemotherapy. Ninety-four percent (94 %) of patients received anthracycline and taxane. Twenty-six (26 %) of patients overall had received prior platinum for breast cancer. In the olaparib and placebo arms, 87 % and 92 % of patients with HR positive disease were receiving concomitant endocrine therapy, respectively.

The study demonstrated a statistically significant and clinically meaningful improvement in IDFS in the olaparib arm compared with the placebo arm. Two hundred and eighty-four (284) patients had IDFS events, this represented 12 % of patients in the olaparib arm (distant 8 %, local/regional 1,4 %, contralateral invasive breast cancer 0,9 %, non-breast second primary malignancies 1,2 %, death 0,2 %) and 20 % of patients in the placebo arm (distant 13 %, local/regional 2,7 %, contralateral invasive breast cancer 1,3 %, non-breast second primary

malignancies 2,3 %, death 0 %). A statistically significant and clinically meaningful improvement in DDFS in the olaparib arm compared with the placebo arm was also observed. At the next planned OS analysis, a statistically significant improvement in OS was observed in the olaparib arm compared with the placebo arm.

VIOLETTE study in metastatic triple negative breast cancer

VIOLETTE was a Phase II, open-label, multicentre study to assess the safety and efficacy of agents targeting DNA damage repair in combination with olaparib versus olaparib monotherapy in the treatment of second or third line metastatic TNBC patients stratified by alterations in HRR-related genes (including *BRCA1/2*).

Thirty-six patients with t*BRCAm* were enrolled to the olaparib monotherapy arm. Confirmed responses were reported in 11 of 33 patients receiving olaparib monotherapy (ORR, 33 % CI 18 – 52 %); median PFS was 6,1 months (95 % CI, 5,1 to 8,9 months). Four patients had somatic *BRCAm* tumours and 2 out of 4 (50 %) had confirmed responses on olaparib.

Germline *BRCA*-mutated HER2-negative metastatic breast cancer

OlympiAD in HER2-negative metastatic breast cancer patients with a gBRCA mutation

The study was a Phase III randomised, open-label, controlled trial that compared the efficacy of olaparib (300 mg [2 x 150 mg tablets] twice daily) taken to progression with a comparator arm of medical practitioner's choice of chemotherapy (capecitabine, eribulin or vinorelbine). In the study 302 patients with *gBRCAm* HER2- negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease were randomised (2:1 randomisation: 205 olaparib and 97 comparator). Patients were stratified based on: receipt of prior chemotherapy regimens for metastatic breast cancer, oestrogen receptor (ER) and / or progesterone receptor (PgR) positive vs ER and PgR negative, prior platinum for breast cancer. The primary endpoint was PFS assessed by BICR using RECIST 1.1. Secondary endpoints included PFS2, OS, objective response rate (ORR) and HRQoL.

All patients had received prior treatment with anthracycline (unless contraindicated) and a taxane in either the neoadjuvant, adjuvant or metastatic setting. Prior therapy with platinum for metastatic breast cancer was allowed provided there had been no evidence of disease progression during platinum treatment. Prior therapy with platinum in the (neo)adjuvant setting was allowed provided the last dose was received at least 12 months prior to randomisation. Patients could not have received prior olaparib or other PARP inhibitor treatment.

Patients with ER and/or PgR positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or had disease that the treating medical practitioner believed to be inappropriate for endocrine therapy. Patients had tumour assessments at baseline and every 6 weeks for the first 24 weeks, and then every 12 weeks relative to date of randomisation, until objective radiological disease progression.
The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS for olaparib-treated patients compared with those in the comparator arm with a HR of 0,58 (95 % CI 0,43 – 0,80; p = 0,0009; median 7,0 months for olaparib vs. 4,2 months for comparator).

A clinically meaningful and statistically significant improvement in PFS2 was also observed with a HR of 0,57 (95 % CI 0,40 – 0,83; p = 0,0033; median 13,2 months for olaparib vs 9,3 months for comparator) indicating that the benefit observed with olaparib continued to be evident even with the use of subsequent therapies. In the measurable disease patient population (77 %), ORR in olaparib-treated patients was 60 % (95 % CI 52,0 – 67,4) and in patients who received comparator was 29 % (95 % CI 18,3 – 41,3). The median time to onset of response was 47 days for olaparib vs 45 days for comparator.

The median duration of response was 6,4 months for olaparib vs 7,1 months for comparator. Overall survival was 64 % mature at the time of the final OS analysis (DCO 25 September

2017). The OS HR comparing olaparib with comparator was 0,90 (95 % CI 0,66 – 1,23; p = 0,5131; median 19,3 months for olaparib vs. 17,1 months for comparator). The median follow-up time in censored patients was 25,3 months for olaparib vs 26,3 months for comparator. Consistent results were observed across patient subgroups.

A significant difference in global health status/QoL (assessed using the EORTC QLQ-C30 questionnaire which uses a 0 – 100 point scale) in favour of olaparib was observed (adjusted mean difference in change from baseline score was 7,5 points [95 % CI: 2,48 – 12,44; p = 0,0035]).

Time to deterioration (≥ 10 points decrease from baseline) in global health status/QoL score was statistically significantly longer on the olaparib arm (HR 0,44; 95 % CI: 0,25 – 0,77; p = 0,0043; median not reached for olaparib vs. 15,3 months for comparator arm). Over the treatment period, the proportion of patients with clinically significant improvement (≥ 10 points increase from baseline) in global health status/QoL score was 33,7 % (n=69) in the olaparib arm and 13,4 % (n=13) in the comparator arm.

Maintenance following first-line treatment of germline *BRCA*-mutated metastatic adenocarcinoma of the pancreas

POLO was a Phase III, randomised, double-blind, placebo-controlled, multicentre trial that compared the efficacy and safety of LYNPARZA maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) with placebo in g*BRCA1/2*-mutated metastatic adenocarcinoma of the pancreas. The study randomised 154 patients with germline *BRCA*1/2 (3:2 randomisation: 92 olaparib and 62 placebo) whose disease had not progressed following at least 16 weeks of first-line platinum-based chemotherapy. There was no upper limit to the duration of chemotherapy received. After 16 weeks of continuous platinum-based chemotherapy, the platinum could be discontinued at any time for toxicity and the other agents continued; the patients were eligible for randomisation as long as there was no evidence of progression at any time during chemotherapy treatment. All toxicities from previous anti-cancer therapy must

have been resolved to CTCAE grade 1, except for alopecia, grade 3 peripheral neuropathy and Hgb ≥ 9 g/dL. LYNPARZA treatment was continued until progression of the underlying disease.

Patients with germline *BRCA* mutations were identified from prior local testing results or by central testing using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test. The *BRCAm* status of all patients identified using prior local testing results was confirmed, where sent, using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test.

Demographic and baseline characteristics were generally well balanced between the olaparib and placebo arms. Median age was 57 years in both arms; 30 % of patients in the olaparib arm were ≥ 65 years compared to 21 % in the placebo arm. Fifty-eight per-cent (58 %) of patients in the olaparib arm and 50% of patients in the placebo group were male. In the olaparib arm 89 % were white and 11 % were non-white. Most patients were ECOG performance status 0 (67 %). Overall, the sites of metastasis prior to chemotherapy were liver (72 %), lung (10%) and other sites (50 %). Ninety-six per-cent (96 %) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy. The median time from initiation of first-line platinum-based chemotherapy to randomisation was 5,8 months (range 3,4 to 33,4 months) and 49 % of patients were in complete or partial response to their most recent platinum-based regimen.

The primary endpoint was progression-free survival (PFS), defined as time from randomisation to progression determined by BICR using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1,1, or death. Secondary efficacy endpoints included overall survival (OS), time from randomisation to second progression or death (PFS2), time from randomisation to first subsequent anti-cancer therapy or death (TFST), time from

randomisation to discontinuation of treatment or death (TDT), objective response rate (ORR), duration of response (DoR), response rate, time to response and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 8 weeks for 40 weeks, and then every 12 weeks relative to the date of randomisation, until objective radiological disease progression. For PFS, the median follow-up time for censored patients was 9,1 months in the olaparib arm and 3,8 months in the placebo arm. For OS, the median follow-up time for censored patients was 31,3 months in the olaparib arm and 23,9 months in the placebo arm.

The study demonstrated a clinically meaningful and statistically significant improvement in PFS for olaparib compared to placebo, with a HR of 0,53 (95 % CI 0,35 – 0,82; p = 0,0038; the median was 7,4 months for olaparib vs 3,8 months for placebo). The sensitivity analysis of PFS by investigator assessment (HR 0,51; 95 % CI 0,34 to 0,78; p = 0,0017; median 6,3 months vs 3,7 months for olaparib vs placebo, respectively) was consistent with the PFS analysis by BICR. Based on Kaplan–Meier estimates, the proportion of patients that were alive and progression-free at 12, 24 and 36 months were 34 %, 28 % and 22 % for olaparib vs 15 %, 10 % and 10 % for placebo.
At the time of PFS analysis the median DoR was longer in the olaparib arm (24,9 months) compared to the placebo arm (3,7 months), with a longer median time to onset of response (5,4 months for olaparib vs 3,6 months for placebo).

At the final analysis of OS (70 % maturity) the HR for OS was 0,83 (95 % CI 0,56 to 1,22; p = 0,3487; median 19,0 months for olaparib vs 19,2 months for placebo) which did not reach statistical significance. The percentage of patients that were alive and in follow-up were 28 % in the olaparib arm and 18 % in the placebo arm.

At the time of final OS analysis, the HR for PFS2 (60 % maturity, not controlled for multiplicity) was 0,66 (95 % CI 0,42 – 1,02; p = 0,0613) with a difference in median of 7,6 months in favour of olaparib (median 16,9 months for olaparib vs 9,3 months for placebo). A clinically

meaningful and statistically significant improvement in TFST and TDT was observed for olaparib-treated patients.

Homologous recombination repair gene mutated metastatic castration-resistant prostate cancer

PROfound was a Phase III randomised, open-label, multicentre trial that evaluated the efficacy of LYNPARZA (300 mg [2 x 150 mg tablets] twice daily) versus a comparator arm of investigator's choice of NHA ([new hormonal agent] enzalutamide or abiraterone acetate) in men with metastatic castration-resistant prostate cancer (mCRPC). Patients needed to have progressed on prior NHA for the treatment of metastatic prostate cancer and/or CRPC and have a tumour mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway. All patients continued on a luteinising hormone releasing hormone (LHRH) analogue or had prior bilateral orchiectomy.

Patients were divided into two cohorts based on HRR gene mutation status. Patients with mutations in either *BRCA1*, *BRCA2 genes* or *ATM mutations* were randomised in Cohort A; patients with mutations among 12 other genes involved in the HRR pathway (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* or *RAD54L*) were randomised in Cohort B. Patients with co-mutations (*BRCA1*, *BRCA2* or *ATM* plus a Cohort B gene) were randomised in Cohort A. Although patients with *PPP2R2A* gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavourable benefit-risk.

The study randomised 387 patients (2:1 randomisation: 256 olaparib and 131 comparator); in Cohort A there were 245 patients (162 olaparib and 83 comparator) and in Cohort B there were 142 patients (94 olaparib and 48 comparator). Patients were stratified by prior taxane use and evidence of measurable disease. Treatment was continued until disease progression. Patients randomised to comparator were given the option to switch to olaparib upon confirmed radiological BICR progression.

Patients with HRR gene mutations were identified based on prostate cancer tissue specimen testing by the Foundation Medicine FoundationOne® HRR clinical trial assay performed in a CLIA certified laboratory (CLIA HRR Clinical Trial Assay) or from reanalysis of data from a prior Foundation Medicine test.

Demographics and baseline characteristics were generally well balanced between the olaparib and comparator arms in Cohort A+B. Median age was 69 years in both arms. Prior therapy in the olaparib arm was 66 % taxane, 40 % enzalutamide, 38 % abiraterone acetate and 20 % both enzalutamide and abiraterone acetate. Prior therapy in the comparator arm was 63 % taxane, 41 % enzalutamide, 41 % abiraterone acetate and 18 % both enzalutamide and abiraterone acetate. Fifty-eight percent (58 %) of patients in the olaparib arm and 55 % in the comparator arm had measurable disease at study entry. The proportion of patients with bone, distant lymph node, locoregional lymph node, liver and respiratory metastases was 85 %, 39 %, 21 %, 10 % and 17 %, respectively in the olaparib arm and 86 %, 39 %, 24 %, 14 % and 12 %, respectively in the comparator arm. Most patients in both treatment arms had an ECOG of 0 or 1 (95 %). Baseline pain scores (BPI-SF worst pain) were 0 – < 2 (48 %), 2 – 3 (12 %) or > 3 (36 %) in the olaparib arm and 0 – < 2 (44 %), 2 – 3 (10 %) or > 3 (43 %) in the comparator arm. Median baseline PSA was 68,22 µg/L in the olaparib arm and 106,49 µg/L in the comparator arm.

The primary endpoint of the study was radiological progression free survival (rPFS) in Cohort A determined by BICR using RECIST 1.1 (soft tissue) and Prostate Cancer Working Group (PCWG3) (bone). Key secondary endpoints included confirmed objective response rate (ORR) by BICR (Cohort A), rPFS by BICR (Cohort A+B), time to pain progression (TTPP) (Cohort A) and overall survival (OS) (Cohort A).

Other secondary endpoints in Cohort A and Cohort A+B included time to first symptomatic skeletal-related event (SSRE), duration of response (DoR), time to opiate use for cancer-related pain, confirmed soft tissue ORR, reduction of at least 50% in the concentration of

prostate specific antigen (PSA_{50}-response), circulating tumour cells (CTC) conversion rate, time to second progression or death (PFS2) and disease-related symptoms and health related quality of life ([HRQoL], pain progression, pain severity progression, pain interference and pain palliation). Other secondary end-points in Cohort B included rPFS by BICR. In addition, other secondary end-points in Cohort B and Cohort A+B included confirmed ORR by BICR, OS and time to pain progression.

The study demonstrated a clinically meaningful and statistically significant improvement in BICR assessed rPFS for olaparib vs comparator in Cohort A and also in Cohort A+B.

In Cohort A there was a statistically significant and clinically meaningful improvement in confirmed radiological ORR by BICR for patients with measurable disease at baseline in the olaparib arm vs comparator and an improvement observed in confirmed radiological ORR Cohort A+B. There was a statistically significant and clinical meaningful delay in TTPP in the olaparib arm compared with the investigators choice of NHA arm in Cohort A and the results in Cohort A+B were consistent with Cohort A.

The final analysis of OS demonstrated a statistically significant improvement in OS in patients randomised to LYNPARZA compared to patients in the investigators choice of NHA arm in Cohort A.

In Cohort B, the median rPFS was 4,8 months for olaparib vs 3,3 months for comparator with a HR of 0,88 (95 % CI 0,58, 1,36; p = 0,3976 [nominal]). Two patients (3,7 %) in the olaparib arm and 2 patients (8,3 %) in the comparator arm with measurable disease at baseline had a confirmed radiological objective response. The odds ratio (OR) and 95 % CIs were not calculated due to the small number of responders. In the olaparib arm, the 2 patients had *CDK12* mutations and achieved a partial response. In the comparator arm, the 2 patients had co-occurring mutations (one with *PALB2*+*PPP2R2A* and one with *CDK12*+*PALB2*) and achieved a partial response. Stable disease was observed in 57,4 % of patients in the olaparib arm and 29,2 % of patients in the comparator arm. The final OS analysis had events in

100/142 patients. Median OS was 14,1 months for olaparib vs 11,5 months for comparator with a HR of 0,96 (95 % CI 0,63, 1,49; p = 0,7921, nominal). The HR indicates no detriment in OS for olaparib-treated patients.

With regards to the rPFS subgroup analysis by Cohort B gene, there was a trend for benefit of olaparib over comparator for patients with a single *CDK12* mutation. For *CHEK2* and *RAD54L*, results should be interpreted with caution due to the small number of events. Hazard ratios were not calculable for some of the Cohort B genes (*BARD1*, *BRIP1*, *CHEK1*, *PALB2*, *RAD51B*, and *RAD51D*) due to the small number of events in these subgroups. In Cohort B a subgroup analysis of confirmed ORR for each individual gene in patients with single HRR gene mutations *CDK12*m patients (5,9 %) in the olaparib arm and no patients in the comparator arm (N=12) had a response The OR and 95 % CIs were not calculable.

Olaparib improved overall adjusted mean change (based in mixed model of repeated measures analysis) from baseline scores in HRQoL (FACT-P total score, FACT-General total score, Trial Outcome Index), functioning (physical well-being, functional well-being) and prostate cancer symptoms (PCS, FACT Advanced Prostate Symptom Index-6) compared with investigators choice of NHA during treatment demonstrating that patients in the olaparib arm experienced improvement in HRQoL, functioning and prostate cancer symptoms compared with patients in the investigators choice of NHA arm in Cohort A. The analysis of adjusted mean change from baseline in HRQoL, functioning and prostate cancer symptoms scores in Cohort A were consistent with results in Cohort A+B.

Treatment of metastatic castration-resistant prostate cancer

The efficacy of Lynparza in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) was investigated in two randomized, double-blind, placebo-controlled trials in the first-line mCRPC setting (PROpel) and in patients who had received prior taxane (Study 8) in the mCRPC setting. In both studies, LYNPARZA was used in combination with abiraterone and prednisone or prednisolone.

PROpel Study in the first-line mCRPC setting

PROpel was a Phase III randomised, double-blind, placebo-controlled, multicentre study that compared the efficacy of Lynparza (300 mg [2 x 150 mg tablets] twice daily) in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily) compared with placebo plus abiraterone for the treatment of patients with mCRPC. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily. Prior to the mCRPC stage, treatment with NHAs (except abiraterone) without PSA progression (clinical or radiological) during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation. Treatment with first-generation antiandrogen agents (e.g., bicalutamide, nilutamide, flutamide) was also allowed, provided there was a washout period of 4 weeks. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at metastatic hormone-sensitive prostate cancer (mHSPC) stage, as long as no signs of disease progression occurred during or immediately after such treatment. All patients continued on a gonadotropin-releasing hormone (GnRH) analogue or had prior bilateral orchiectomy.

The study randomised 796 patients (1:1 randomisation; 399 olaparib/abiraterone: 397 placebo/abiraterone) who had evidence of histologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan. Patients were stratified by metastases (bone only, visceral or other) and docetaxel treatment at mHSPC stage (yes or no).

Treatment was continued until disease progression or unacceptable toxicity.

Demographic and baseline characteristics were well balanced between both arms. The median age of patients was 69 years, and the majority (71 %) of patients were in the ≥ 65 years age group. Twenty-one (21) (3 %) patients had prior docetaxel treatment during neoadjuvant/adjuvant treatment for localised prostate cancer and 179 (22 %) patients had prior docetaxel treatment at mHSPC stage. The majority of patients in both arms were ECOG performance status 0 (70 %).

HRR gene mutation status was assessed retrospectively by ctDNA and tumour tissue tests. Of the patients tested, 198 and 118 were HRRm as determined by ctDNA and tumour tissue, respectively. The distribution of HRRm patients was well balanced between the two arms.

The primary endpoint was rPFS, defined as time from randomisation to progression determined by investigator assessment based on RECIST 1.1 and PCWG-3 criteria (bone). The key secondary efficacy endpoint was overall survival (OS). Additional secondary endpoints included PFS2, TFST and HRQoL.

At the time of interim rPFS analysis, there was a statistically significant and clinically meaningful improvement in the risk of radiological disease progression or death for olaparib/abiraterone compared to placebo/abiraterone as assessed by the investigator. The sensitivity analysis of rPFS by BICR was consistent with the investigator-based analysis with HR 0,61; 95 % CI 0,49, 0,74; p < 0,0001; median rPFS 27,6 months in the olaparib/abiraterone arm vs 16,4 months in the placebo/abiraterone arm, respectively.

Subgroup analysis showed rPFS improvement for olaparib/abiraterone compared to placebo/abiraterone in all pre-defined sub-groups, including patients with or without prior taxane at mHSPC, patients with different metastatic disease at baseline (bone only vs visceral vs other) and patients with or without HRRm.

There were improvements in PFS2 and TFST in the olaparib/abiraterone arm vs. placebo/abiraterone arm.

At the final prespecified analysis, the percentage of patients alive at 36 months in the olaparib/abiraterone arm and the placebo/abiraterone arm was 57 % and 50 %, respectively.

Study 8 in patients who had received prior taxane in the mCRPC setting

Study 8 was a two-part study. Part A was an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics of olaparib when given in addition to abiraterone

1000 mg once daily. Part B was a Phase II, randomised, double-blind, placebo-controlled, multicentre study that compared the efficacy of Lynparza (300 mg [2 x 150 mg tablets] twice daily) in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily) compared with placebo and abiraterone in patients with mCRPC who had received up to two lines of prior chemotherapy including docetaxel but no prior exposure to NHA. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily. Patients who discontinued docetaxel for toxicity reasons and without completing the full course were still eligible to enter this study provided they received at least 2 cycles of chemotherapy. All patients continued on a GnRH analogue or had bilateral orchiectomy. Of the 171 patients enrolled in Part B, 142 patients were randomised (1:1 randomisation; 71 olaparib/abiraterone:71 placebo/abiraterone). All of the randomised patients received at least one dose of study treatment.

The primary endpoint of the study (Part B) was rPFS determined by investigator using RECIST 1.1 (soft tissue) and PCWG-2 (bone). Secondary endpoints included PFS2, OS and TFST.

The study demonstrated a statistically significant and clinically meaningful improvement in the investigator-assessed rPFS olaparib/abiraterone arm compared to the placebo/abiraterone arm.

Subgroup analyses for subsets of patients based on demographic, baseline characteristics and pre-defined biomarker subgroups showed generally consistent reductions in the risk of radiological progression or death in olaparib/abiraterone-treated patients across the subgroups, in patients with or without HRRm.

The results from the secondary endpoints, including PFS2, TFST and OS also favoured olaparib/abiraterone arm.

Effect on the QT interval

There is no clinically relevant effect of olaparib on cardiac repolarisation (as evaluated by an effect on the QT interval) following 300 mg twice daily multiple dosing of olaparib.

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 treatment ratio: 1,08; 90 % CI: 1,01, 1,16). Consequently, patients should take LYNPARZA without regard to food (see section 4.2).

Distribution

The *in vitro* plasma protein binding is approximately 82 % at 10 µg/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 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. Following oral dosing of 14C-olaparib to female patients, unchanged olaparib accounted for the majority of the circulating radioactivity in plasma (70 %) and was the major component found in both urine and faeces (15 % and 6 % of the dose respectively). The metabolism of olaparib is extensive with the main site of metabolism being the piperazine and fluorobenzyl ring structures. The majority of the metabolism was attributable to oxidation reactions with a number of the components produced undergoing subsequent glucuronide or sulphate conjugation. Up to 20, 37 and 20 metabolites were detected in plasma, urine and faeces respectively, the majority of them representing <1 % of the dosed material. A ring-open 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 UGT1A4, UGT1A9, UGT2B7, or CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes. Olaparib inhibited UGT1A1 *in vitro*, however, PBPK simulations suggest this is not of clinical importance.

Based on evaluation using enzyme activity, olaparib was not an inducer of CYP2C9 or 2C19. *In vitro*, olaparib is a substrate of and inhibits the efflux transporter P-gp (IC50 = 76μM), however, this is unlikely to be of clinical significance.

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

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. The majority of the material was excreted as metabolites.

Special populations

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

Renal impairment

Following a single oral 300 mg dose of olaparib to patients with mild renal impairment (creatinine clearance: 51 to 80 mL/min), AUC increased by 24 % and C_{max} by 15 % compared with patients with normal renal function. No LYNPARZA dose adjustment is required for patients with mild renal impairment.

Following a single oral 300 mg dose of olaparib to patients with moderate renal impairment (creatinine clearance: 31 to 50 mL/min), AUC increased by 44 % and C_{max} by 26 % compared with patients with normal renal function. LYNPARZA dose adjustment is recommended for patients with moderate renal impairment (see section 4.2).

Olaparib has not been studied in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤ 30 mL/min).

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Copovidone

Colloidal silicon dioxide

Mannitol

Sodium stearyl fumarate

Tablet coating:

Hypromellose

Macrogol 400

Titanium dioxide (E171)

Iron oxide yellow (E172)

Iron oxide black (E172) (LYNPARZA 150 mg tablet only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 30 °C.

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

6.5 Nature and contents of container

Aluminium/Aluminium non-perforated blister containing 8 tablets.

Cartons of 56 tablets (7 blisters) and a multipack containing 112 (2 cartons of 56) tablets.

HDPE bottle containing desiccant with a child-resistant closure. Pack sizes of 60 or 120

tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Ltd

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

TEL: +27 (0) 11 797-6000

8. REGISTRATION NUMBERS

LYNPARZA 100: 52/26/0745

LYNPARZA 150: 52/26/0746

9. DATE OF FIRST AUTHORISATION

04 May 2021

10. DATE OF REVISION OF THE TEXT

19 June 2026