Summary of Product Characteristics

1. Name of the Drug Product

Olaparix 150 Tablet

2. Qualitative and Quantitative Composition

SN	Name of Materials	Specification	Quantity/ Tablet	Function
	ACTIVE SUBSTANCE:			
01	Olaparib (Micronised)*	INN	150.000 mg	Active Material
	EXCIPIENTS:			
02	Pregelatinised Starch (Starch 1500)	BP	78.000 mg	Binder
03	Copovidone (Kollidon VA 64)	BP	48.750 mg	Binder
04	Sodium Starch Glycolate (Primojel)	BP	58.500 mg	Disintegrant
05	Polacrilin Potassium (Kyron –T314)	USP-NF	78.000 mg	Dissolution Enhancer
06	Sodium Stearyl Fumarate	BP	19.500 mg	Lubricant
07	Colloidal Anhydrous Silica (Aerosil 200)	BP	9.750 mg	Glidant
08	Mannitol (DC Grade)	BP	243.750 mg	Diluent
09	Microcrystalline Cellulose (Avicel PH 102)**	BP	288.750 mg	Diluent
	COATING MATERIALS:			
10	Opadry (03B530102) Orange	Ph. Grade	34.125 mg	Coating Agent
11	Ethanol (96%)***	USP	409.500 mg	Solvent

Note:

* Based on 100% potency

** Calculated amount of material

*** *** Solvent does not appear in the final product

3. Pharmaceutical Form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

Ovarian cancer

Olaparib is indicated as monotherapy for the:

• Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary

peritoneal cancer who are in response (complete or partial) following completion of 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 or partial) to platinum-based chemotherapy.

Breast cancer

Olaparib is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo) adjuvant or metastatic setting unless patients were not suitable for these treatments.

Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

4.2 Posology and method of administration

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

Detection of *BRCA1/2* mutations

Before Olaparib treatment is initiated for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC), patients must have confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the breast cancer susceptibility genes (*BRCA*) 1 or 2 using a validated test.

There is no requirement for *BRCA1/2* testing prior to using Olaparib for the maintenance treatment of relapsed EOC, FTC or PPC who are in a complete or partial response to platinum-based therapy.

For germline breast cancer susceptibility genes (*gBRCA1/2*) mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious *gBRCA1/2* mutation before Olaparib treatment is initiated. *gBRCA1/2* mutation status should be determined by an experienced laboratory using a validated test method. Data demonstrating clinical validation of tumour *BRCA1/2* tests in breast cancer are not currently available.

Genetic counselling for patients tested for mutations in *BRCA1/2* genes should be performed according to local regulations.

Posology

Olaparib is available as 50 mg capsule and 150 mg tablets.

The recommended dose of Olaparib is 300 mg, taken twice daily, equivalent to a total daily dose of 600 mg.

Patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based

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

Duration of treatment

First-line maintenance treatment of BRCA-mutated advanced ovarian cancer:

Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

Maintenance treatment of platinum sensitive relapsed ovarian cancer:

For patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

gBRCA1/2-mutated HER2-negative metastatic breast cancer:

It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

There are no efficacy or safety data on maintenance retreatment with Olaparib following first or subsequent relapse in ovarian cancer patients or on retreatment of breast cancer patients.

Important differences in posology between Olaparib tablets and capsules

Olaparib tablets (150 mg) should not be substituted for Olaparib 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 Olaparib, 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. The recommended dose reduction is to 250 mg twice daily (equivalent to a total daily dose of 500 mg).

If a further dose reduction is required, then reduction to 200 mg 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 Olaparib dose reduction is to 100 mg taken twice daily (equivalent to a total daily dose of 200 mg). If a moderate CYP3A inhibitor must be co-administered, the recommended

Olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg).

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 Olaparib is 200 mg twice daily (equivalent to a total daily dose of 400 mg).

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

Olaparib is not recommended for use in 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. Olaparib 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

Olaparib can be administered to patients with mild or moderate hepatic impairment (Child-Pugh classification A or B) with no dose adjustment. Olaparib 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.

Paediatric population

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

No data are available.

Method of administration

Olaparib is for oral use.

Olaparib Capsules should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib capsules 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 1 month after the last dose.

4.4 Special warnings and precautions for use

Haematological toxicity

Haematological toxicity has been reported in patients treated with Olaparib, including clinical diagnoses and/or laboratory findings of generally mild or moderate (CTCAE grade 1 or 2) anaemia, neutropenia, thrombocytopenia and lymphopenia. Patients should not start treatment with Olaparib until they have recovered from haematological toxicity caused by previous anticancer 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.

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

Myelodysplastic syndrome/Acute myeloid leukaemia

The overall incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Olaparib 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 (g*BRCA1/2*) mutation carriers. The incidence of MDS/AML cases was similar among g*BRCA1m* and g*BRCA2m* patients (1.7% and 1.4%, respectively). 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 Olaparib, it is recommended that Olaparib 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 Olaparib 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, Olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, Olaparib treatment should be discontinued and the patient treated appropriately.

Embryofoetal toxicity

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

Pregnancy/contraception

Olaparib should not be used during pregnancy. Women of childbearing potential must use two forms of reliable contraception before starting Olaparib treatment, during therapy and for 1 month after receiving the last dose of Olaparib . Two highly effective and complementary forms of contraception are recommended.

Interactions

Olaparib co-administration with strong or moderate CYP3A inhibitors is not recommended. If a strong or moderate CYP3A inhibitor must be co-administered, the dose of Olaparib should be reduced.

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

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 Olaparib 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 Olaparib 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 Olaparib. If strong or moderate CYP3A inhibitors must be co-administered, the dose of Olaparib should be reduced. The recommended Olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a strong CYP3A inhibitor or 200 mg taken twice daily (equivalent to a total daily dose

of 400 mg) with a moderate CYP3A inhibitor . It is also not recommended to consume grapefruit juice while on Olaparib 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 Olaparib, as it is possible that the efficacy of Olaparib could be substantially reduced. The magnitude of the effect of moderate to strong inducers (e.g. efavirenz, rifabutin) on olaparib exposure is not established, therefore the co-administration of Olaparib with these medicinal products is also not recommended.

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 (IC50 = 76µM), therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp (e.g. simvastatin, pravastatin, dabigatran, digoxin and colchicine). Appropriate clinical monitoring is recommended for patients receiving this type of 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 Olaparib and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment and considered regularly throughout treatment.

Women of childbearing potential must use two forms of reliable contraception before starting Olaparib therapy, during therapy and for 1 month after receiving the last dose of Olaparib, unless abstinence is the chosen method of contraception. Two highly effective and complementary forms of contraception are recommended.

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 should be considered during treatment. For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

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. There are no data from the use of olaparib in pregnant women, however, based on the mode of action of olaparib, Olaparib 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 Olaparib. (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. Olaparib is contraindicated during breast-feeding and for 1 month after receiving the last dose, given the pharmacologic property of the product.

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.

4.7 Effects on ability to drive and use machines

Olaparib has moderate influence on the ability to drive and use machines. Patients who take Olaparib 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

Olaparib monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Olaparib monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache,

dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia.

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (16%), neutropenia (6%), fatigue/asthenia (6%), leukopenia (3%), thrombocytopenia (2%) and vomiting (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions were anaemia (13.9%), vomiting (7.1%), nausea (6.6%), fatigue/asthenia (6.1%) and neutropenia (5.8%). Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.3%), nausea (0.8%) and thrombocytopenia (0.5%).

Tabulated list of adverse reactions

The safety profile is based on pooled data from 1,826 patients with solid tumours treated with Olaparib monotherapy in clinical trials at the recommended dose.

The following adverse reactions have been identified in clinical trials with patients receiving Olaparib 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); 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	**Very common** Anaemia[a], Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common** Lymphopenia[a]	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia[a]
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	-
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness, Headache, Dysgeusia	**Uncommon** Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a]	**Common** Dyspnoea[a] **Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia, Upper abdominal pain **Common** Stomatitis[a]	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis[a], Upper abdominal pain

General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Increase in blood creatinine **Uncommon** Mean corpuscular volume elevation	**Uncommon** Increase in blood creatinine

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased; Neutropenia includes PTs of agranulocytosis, febrile neutropenia, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased; Thrombocytopenia includes PTs of platelet count decreased, platelet production decreased, plateletcrit decrease and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of exfoliative rash, generalised erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular and rash pruritic; Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative. Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.

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, 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%, 5.1% and 0%, respectively; 16.2% 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 Olaparib the incidence of CTCAE grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 20%, 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 .

Other laboratory findings

In clinical studies with Olaparib the incidence of CTCAE grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 10%. 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.

Gastrointestinal toxicities

Nausea was generally reported very early, with first onset within the first month of Olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of Olaparib 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:

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms of overdose are not established and there is no specific treatment in the event of Olaparib 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

Local or central testing of blood or tumour samples for *BRCA1/2* mutations has been used in different studies. Depending on the test used and the international classification consensus, the *BRCA1/2* mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Genetic testing should be conducted by an experienced laboratory using a 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. Most patients were ECOG performance status 0 (77%), there are no data in patients with performance status 2 to 4.

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 *BRCA*1/2 mutation (*BRCA* mutation status for some patients was determined retrospectively). There are limited data in patients with somatic *BRCA* mutated tumours; 10 patients in the olaparib arm and 10 patients in the placebo arm were defined as having somatic *BRCA*1/2 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			

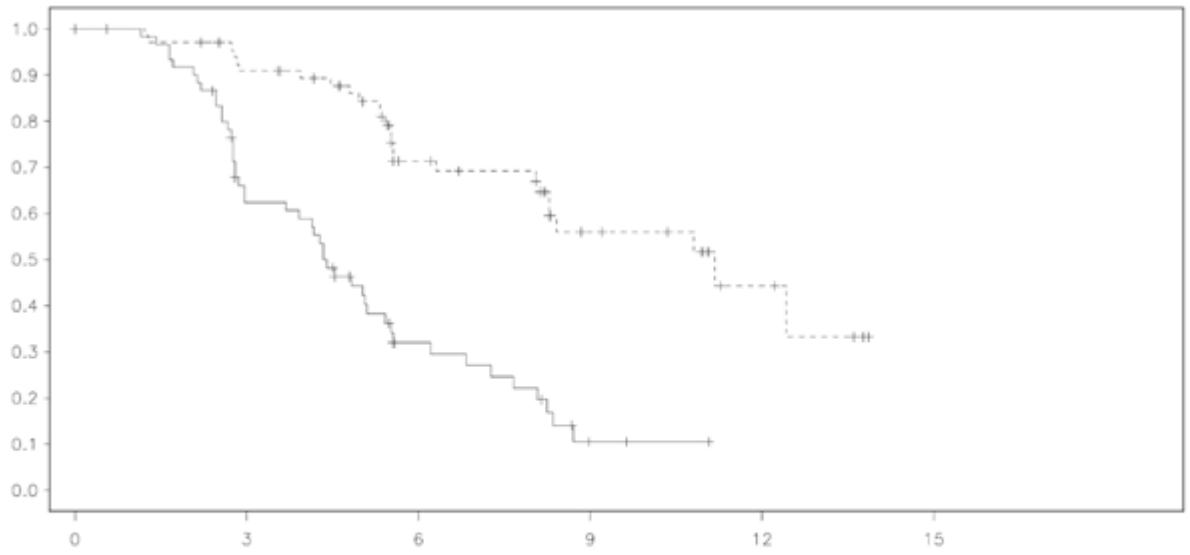
* There was no strategy for multiple testing in place for the sub-group analyses.

[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.

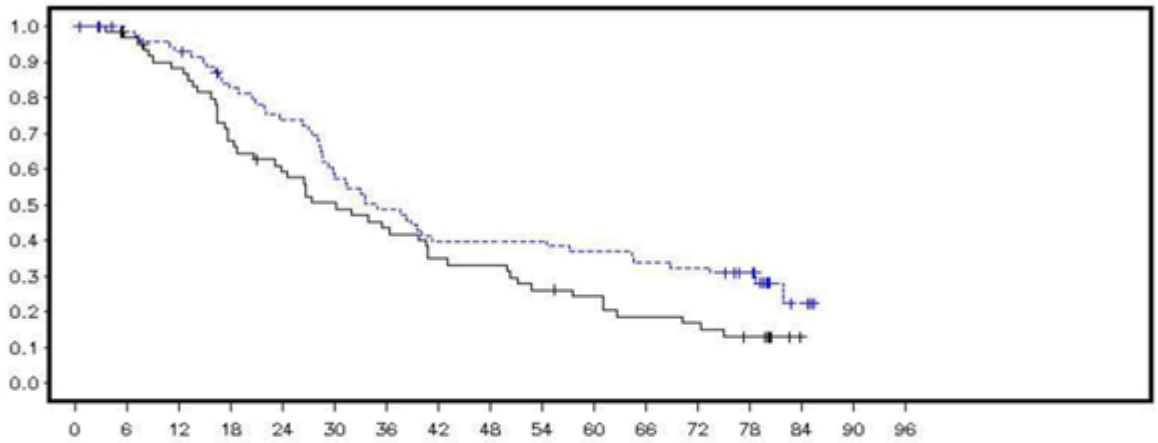
Figure 1 Study 19: Kaplan-Meier plot of PFS in *BRCA*-mutated patients (53% maturity-investigator assessment)



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: s*BRCA* 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 Olaparib in all subsets of the paediatric population, in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours).

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 Olaparib at least one hour after food, and refrain from eating preferably for up to 2 hours afterwards.

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.

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 ~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 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 .

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

Special populations

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 Olaparib 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. Olaparib dose adjustment is recommended for patients with moderate renal impairment.

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 Olaparib dose adjustment is required for patients with mild or moderate hepatic impairment. 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 contents:

Pregelatinised Starch (Starch 1500)
Copovidone (Kollidon VA 64)
Sodium Starch Glycolate (Primojel)
Polacrilin Potassium (Kyron –T314)
Sodium Stearyl Fumarate
Colloidal Anhydrous Silica (Aerosil 200)
Mannitol (DC Grade)
Microcrystalline Cellulose (Avicel PH 102)**
Opadry (03B530102) Orange
Ethanol (96%)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a cool and dry place (below 30°C), away from light. Keep out of the reach of Children.

6.5 Nature and contents of container

Primary Packaging: HDPE bottle

Secondary Packaging: Paper board carton

Pack size: 1 × 120’s tablets in Box

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

CORPORATE OFFICE

Beacon Business Center

9/B/2, Toyenbee Circular Road, Motijheel, Dhaka- 1223, Bangladesh

Tel: +880-2-5716371-76,

Fax: 880-2-57165379

E-mail: beacon@beaconpharma.com.bd

Website: www. beaconpharma.com.bd

FACTORY

Bhaluka, Mymensingh, Bangladesh

8. Marketing authorization Number:

M.A No. 341-395-010

9. Date of first authorization/renewal of the authorization

16.09.2019/ 15.09.2024

10. Date of revision of the text

01.10.2019