

For the use of Registered Medical Practitioner only (Oncologist only)

1. Generic Name & Brand Name

Olaparib Tablets 100 mg

Parbraze™ 100

Olaparib Tablets 150 mg

Parbraze™ 150

2. Qualitative and Quantitative Composition:

Parbraze™ 100

Each film coated tablet contains:

Olaparib100 mg

Excipients q.s.

Colour: Titanium Dioxide I.P.

Parbraze™ 150

Each film coated tablet contains:

Olaparib150 mg

Excipients q.s.

Colour: Titanium Dioxide I.P.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy.
- In patients with deleterious or suspected deleterious gBRCAm, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment.
- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.

4.2 Posology and method of administration

Posology

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

Patient selection

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

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.

Maintenance treatment of platinum-sensitive relapsed ovarian cancer:

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

First-line maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab:

Before Olaparib with bevacizumab treatment is initiated for the first-line maintenance treatment of EOC, FTC or PPC, patients must have confirmation of either deleterious or suspected deleterious *BRCA1/2* mutation and/or genomic instability determined using a validated test.

Adjuvant treatment of germline BRCA-mutated high risk early breast cancer

Before Olaparib treatment is initiated for adjuvant treatment of HER2 negative high risk early breast cancer, patients must have confirmation of deleterious or suspected deleterious *gBRCA1/2* mutation using a validated test.

Monotherapy treatment of gBRCA1/2-mutated HER2-negative metastatic breast cancer:

For germline breast cancer susceptibility genes (*gBRCA1/2*) mutated human epidermal growth factor receptor 2 (HER2)-negative locally advanced or 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.

Olaparib is available as 100 mg and 150 mg tablets.

The recommended dose of Olaparib in monotherapy or in combination with bevacizumab for ovarian cancer or endocrine therapy 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.

Olaparib monotherapy

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.

Olaparib in combination with bevacizumab

When Olaparib is used in combination with bevacizumab for the first-line maintenance treatment of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer following completion of first-line platinum-based therapy with bevacizumab, the dose of bevacizumab is 15 mg/kg once every 3 weeks. Please refer to the full product information for bevacizumab.

Olaparib in combination with endocrine therapy

Please refer to the full product information of the endocrine therapy combination partner(s) (aromatase inhibitor/anti-oestrogen agent and/or LHRH) for the recommended posology.

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.

First-line maintenance treatment of HRD positive advanced ovarian cancer in combination with bevacizumab:

Patients can continue treatment with Olaparib 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 Olaparib treatment, can be treated beyond 2 years. Please refer to the product information for bevacizumab for the recommended overall duration of treatment of a maximum of 15 months including the periods in combination with chemotherapy and as maintenance.

Adjuvant treatment of germline BRCA-mutated high risk early breast cancer

It is recommended that patients are treated for up to 1 year, or until disease recurrence, or unacceptable toxicity, whichever occurs first.

Monotherapy treatment of gBRCA1/2-mutated HER2-negative metastatic breast cancer:

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

The efficacy and safety of maintenance retreatment with Olaparib following first or subsequent relapse in ovarian cancer patients has not been established. There are no efficacy or safety data on retreatment of breast cancer patients.

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

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

Dose adjustments for co-administration with CYP3A inhibitors

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

Special Patient Populations

Elderly

No adjustment in starting dose is required for elderly patients.

Renal impairment

For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Olaparib is 200 mg (two 100 mg tablets) 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 tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets may be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding during treatment and for 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 $\leq$ CTCAE grade 1). Baseline testing, followed by monthly monitoring, of complete blood counts is recommended for the first 12 months of treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

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%, with higher incidence in patients with *BRC*Am platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years. 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 >4 years.

If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Olaparib should be discontinued and the patient treated appropriately.

Venous Thromboembolic Events

Venous thromboembolic events, predominantly events of pulmonary embolism, have occurred in patients treated with Olaparib 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.

Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Patients with a prior history of VTE may be more at risk of a further occurrence and should be monitored 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.

Hepatotoxicity

Cases of hepatotoxicity have been reported in patients treated with Olaparib.

If clinical symptoms or signs suggestive of hepatotoxicity develop, prompt clinical evaluation of the patient and measurement of liver function tests should be performed. In case of suspected drug-induced liver injury (DILI), treatment should be interrupted. In case of severe DILI treatment discontinuation should be considered as clinically appropriate.

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 300 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 6 months after receiving the last dose of Olaparib. Two highly effective and complementary forms of contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of Olaparib.

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 Drug Interactions

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 100 mg taken twice daily (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor. 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.

In vitro, Olaparib inhibits the efflux transporter P-gp (IC₅₀=76 µM), 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 clinically relevant interactions were observed.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

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 6 months 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.

Contraception in males

It is not known whether Olaparib 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 Olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use highly effective contraception if they are of childbearing potential. Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of Olaparib.

Pregnancy

Studies in animals have shown reproductive toxicity including serious teratogenic effects and effects on embryofetal 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 6 months after receiving the last dose of Olaparib.

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 embryofetal 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 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 ($\geq 10\%$) were nausea, fatigue/asthenia, anaemia, vomiting, diarrhoea, decreased appetite, headache, neutropenia, dysgeusia, cough, leukopenia, dizziness, dyspnoea and dyspepsia.

The Grade ≥ 3 adverse reactions occurring in $> 2\%$ of patients were anaemia (14%), neutropenia (5%), fatigue/asthenia (4%), leukopenia (2%) and thrombocytopenia (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions in monotherapy were anaemia (16%), nausea (7%), fatigue/asthenia (6%), neutropenia (6%) and vomiting (6%).

Adverse reactions that most commonly led to permanent discontinuation were anaemia (1.7%), nausea (0.9%), fatigue/asthenia (0.8%), thrombocytopenia (0.7%), neutropenia (0.6%) and vomiting (0.5%).

Adverse events led to dose interruption and/ or reduction of Olaparib in 57% of patients when used in combination with bevacizumab and led to permanent discontinuation of treatment with Olaparib/bevacizumab and placebo/bevacizumab in 21% and 6% of patients, respectively. The adverse reactions that most commonly led to dose interruption and/or reduction were anaemia (21.7%), nausea (9.5%), fatigue/asthenia (5.4%), vomiting (3.7%), neutropenia (3.6%),

thrombocytopenia (3.0%) and diarrhoea (2.6%). The adverse reactions that most commonly led to permanent discontinuation were anaemia (3.7%), nausea (3.6%) and fatigue/asthenia (1.5%).

Tabulated list of adverse reactions

The safety profile is based on pooled data from 4499 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); 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
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon Myelodysplastic syndrome/ Acute myeloid leukaemia ^a	Uncommon Myelodysplastic syndrome/ Acute myeloid leukaemia
Blood and lymphatic system disorders ^b	Very common Anaemia ^a , Neutropenia ^a , Leukopenia ^a Common Lymphopenia ^a , Thrombocytopenia ^a	Very common Anaemia ^a Common Neutropenia ^a , Thrombocytopenia ^a , Leukopenia ^a , Lymphopenia ^a

Immune system disorders	Uncommon Hypersensitivity ^a Rare Angioedema*	Rare Hypersensitivity ^a
Hepatobiliary disorders	Common Transaminases increased ^a Not known Drug-induced liver injury*	
Metabolism and nutrition disorders	Very common Decreased appetite	Uncommon Decreased appetite
Nervous system disorders	Very common Dizziness, Headache, Dysgeusia ^a	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 Common Stomatitis ^a , Upper abdominal pain	Common Vomiting, Nausea Uncommon Stomatitis ^a , Diarrhoea Rare Dyspepsia, Upper abdominal pain
Skin and subcutaneous tissue disorders	Common Rash ^a Uncommon Dermatitis ^a Rare Erythema nodosum	Uncommon Rash ^a Rare Dermatitis ^a

General disorders and administration site conditions	Very common Fatigue (including asthenia)	Common Fatigue (including asthenia)
Investigations ^b	Common Blood creatinine increased Uncommon Mean cell volume increased	Rare Blood creatinine increased
Vascular disorders	Common Venous thromboembolism ^a	Common Venous thromboembolism ^a

^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.

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

Lymphopenia includes PTs of lymphocyte count decreased and lymphopenia. Hypersensitivity includes PTs of drug hypersensitivity and hypersensitivity.

Transaminases increased includes PTs of alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and hypertransaminasaemia

Dysgeusia includes PTs of dysgeusia and taste disorder. Cough includes PTs of cough and productive cough.

Dyspnoea includes PTs of dyspnoea and dyspnoea exertional.

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.

Venous thromboembolism includes PTs of embolism, pulmonary embolism, thrombosis, deep vein thrombosis, vena cava thrombosis and venous thrombosis.

^b Registered laboratory data are presented below under *Haematological toxicity* and *Other laboratory findings*.

*As observed in the post-marketing setting.

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 clinical studies with the tablet formulation, the incidence of anaemia adverse reactions was 35.2% (CTCAE grade ≥ 3 14.8%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were 16.4%, 11.1% and 2.1%, respectively; 15.6% of patients treated with Olaparib needed one or more blood transfusions. An exposure-response relationship between Olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with Olaparib 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 ULN 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.

Myelodysplastic syndrome/Acute myeloid leukaemia

MDS/AML are serious adverse reactions that occurred uncommonly in monotherapy clinical studies at the therapeutic dose, across all indications (0.9%). The incidence was 0.5% including events reported during the long-term safety follow up (rate calculated based on overall safety population of 18576 patients exposed to at least one dose of oral Olaparib in clinical studies). All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in germline breast cancer susceptibility gene 1 or 2 (*gBRCA1/2*) mutation carriers. The incidence of MDS/AML cases was similar among *gBRCA1m* and *gBRCA2m* patients (1.6% and 1.2%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia.

In patients with *BRCAm* 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 Olaparib treatment ≥ 2 years in 45% of patients), the incidence of MDS/AML was 8% in patients receiving Olaparib and 4% in patients receiving placebo at a follow-up of 5 years. In the Olaparib arm, 9 out of 16 MDS/AML cases occurred after discontinuation of Olaparib during the survival follow-up. The incidence of MDS/AML was observed in the context of extended overall survival in the Olaparib arm and late onset of MDS/AML. The risk of MDS/AML remains low in the first line setting when Olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years (1.5%) in SOLO1 study at 7 year follow up and 1.1% in PAOLA-1 study at 5 year follow up. For risk mitigation and management.

Venous Thromboembolic Events

In men who received Olaparib plus abiraterone as first line therapy for mCRPC (PROpel study), the incidence of venous thromboembolic events was 8% in the Olaparib plus abiraterone arm, and 3.3% in the placebo plus abiraterone arm. The median time to onset in this study was 170 days (range: 12 to 906 days). The majority of patients recovered from the event and were able to continue Olaparib with standard medical treatment.

Patients with significant cardiovascular disease were excluded.

Other laboratory findings

In clinical studies with Olaparib 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, 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.

In first-line ovarian cancer maintenance treatment, patients experienced nausea events (77% on Olaparib, 38% on placebo), vomiting (40% on Olaparib, 15% on placebo), diarrhoea (34% on Olaparib, 25% on placebo) and dyspepsia (17% on Olaparib, 12% on placebo). Nausea events led to discontinuation in 2.3% of Olaparib-treated patients (CTCAE Grade 2) and 0.8% of placebo-treated patients (CTCAE Grade 1); 0.8% and 0.4% of Olaparib-treated patients discontinued treatment due to low grade (CTCAE Grade 2) vomiting and dyspepsia, respectively. No Olaparib or placebo-treated patients discontinued due to diarrhoea. No placebo-treated patients discontinued due to vomiting or dyspepsia. Nausea events led to dose interruption and dose reductions in 14% and 4%, respectively, of Olaparib-treated patients. Vomiting events led to interruption in 10% of Olaparib-treated patients; no Olaparib-treated patients experienced a vomiting event leading to dose reduction.

Paediatric population

No studies have been conducted in paediatric patients.

Other special populations

Limited safety data are available in non-Caucasian patients.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (form.heteroworld.com) or by **Hetero Helpline No.1800-120-8689** and for all India safety cases and complaints, please write to drugsafetyindia@heterodrugs.com.

4.9 Overdose

There is limited experience of overdose with Olaparib. No unexpected adverse reactions were reported in a small number of patients who took a daily dose of up to 900 mg of Olaparib tablets over two days. Symptoms of overdose are not established and there is no specific treatment in the

event of 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 Mechanism of action

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).

5.2 Pharmacodynamic Properties

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 cancer cells lacking critical functional components for efficient HRR such as BRCA1 or 2, DNA DSBs cannot be repaired accurately or effectively, leading to substantial homologous recombination deficiency (HRD). Instead, alternative and error-prone pathways are activated, such as the classical non-homologous end joining (NHEJ) pathway, leading to a high degree of 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. 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 possibly 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.

Combined anti-tumour effect with NHAs

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.

Detection of *BRCA1/2* mutations

Genetic testing should be conducted by an experienced laboratory using a validated test. Local or central testing of blood and/or tumour samples for germline and/or somatic *BRCA1/2* mutations have been used in different studies. DNA obtained from a tissue or blood sample has been tested in most of the studies, with testing of ctDNA being used for exploratory purposes. 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. Homologous recombination deficiency (HRD) positive status can be defined by detection of a *BRCA1/2* mutation classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Detection of these mutations could be combined with positive HRD score (below) to determine HRD positive status.

Detection of genomic instability

HR deficiency-associated genomic alterations that have been investigated in Paola-1 include genome- wide loss of heterozygosity, telomeric allelic imbalance and large-scale transition, which are continuous measures with pre-defined criteria and score. Composite genomic instability score (GIS, also called HRD score) is determined when the combined measures and respective scores are used to assess the extent of specific genomic aberrations accumulated in tumour cells. Lower score defines lower likelihood of HR deficiency of tumour cells and higher score determines higher likelihood of HR deficiency of tumour cells at the time of the sample collection relative to exposure to DNA damaging agents. Validated cut-offs should be used to determine GIS positive status.

HRD positive status can be defined by a composite GIS score for HR deficiency-associated genomic alterations tested by an experienced laboratory using a validated test.

5.3 Pharmacokinetic properties

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

Absorption

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

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

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.

Metabolism

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).

Excretion

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, gender, bodyweight, tumour location 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 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 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.

Drug Interactions

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 OA P1B1, OATP1B3, OCT1, BCRP or MRP2 and is not an inhibitor of OATP1B3, OAT1 or MRP2.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with Olaparib.

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.

7. Description

Parbraz 100 is supplied for oral administration, as a film-coated tablet of Olaparib. Each film-coated tablet of Parbraz 100 contains Olaparib 100 mg.

Parbraz 150 is supplied for oral administration, as a film-coated tablet of Olaparib. Each film-coated tablet of Parbraz 150 contains Olaparib 150 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition and handling instructions.

Refer Pack

9. Patient Counseling Information

MDS/AML

Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or a more serious uncommon bone marrow problem called ‘myelodysplastic syndrome’ (MDS) or ‘acute myeloid leukemia’ (AML) which have been reported in patients treated with Olaparib.

Pneumonitis

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing

Venous Thromboembolism

Advise patients to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia

Embryo-Fetal Toxicity

Inform pregnant women of the risk to a fetus and potential loss of the pregnancy. Advise females to inform their healthcare provider of known or suspected pregnancy

Advise females of reproductive potential to use effective contraception during treatment with Olaparib and for 6 months after the last dose.

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months after receiving the last dose of Olaparib. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Olaparib.

Lactation

Advise patients not to breastfeed while taking Olaparib and for one month after receiving the last dose.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice while taking Olaparib

Nausea/Vomiting

Advise patients that mild or moderate nausea and/or vomiting is very common in patients receiving Olaparib and that they should contact their healthcare provider who will advise on available antiemetic treatment options.

10. Details of manufacturer

Refer Pack for manufacturer details.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 6 &

11 to 16 Ground Floor, 101 to 106 &

111 to 116 First Floor, 201 to 206 & 211 to 216

2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

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11. Details of permission or licence number

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12. Date of revision

Version 2.0, dated 07/06/2024

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com