Olaparib (Tablet) Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA 1/2-mutated (germline and/or somatic) • High-grade epithelial ovarian • fallopian tube cancer • primary peritoneal carcinoma who are in response (complete or partial) following completion of first-line platinum based chemotherapy	C56 C48 C57	00588a 00588b 00588c	CDS 01/12/2020
Maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) • high grade serous epithelial ovarian cancer • fallopian tube cancer • primary peritoneal cancer who are in response (complete response or partial) to platinum-based chemotherapy	C56 C48 C57	00588d 00588e 00588f	CDS
As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.	C61	00588g	CDS 01/03/2023

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

1L Maintenance treatment of BRCA-mutated advanced ovarian cancer:
Olaparib is taken twice daily continuously 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 BRCA-mutated ovarian cancer:
Olaparib is taken twice daily continuously until disease progression or unacceptable toxicity develops.

Treatment of prostate cancer:
Olaparib is taken twice daily continuously until disease progression or unacceptable toxicity develops. Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

Drug	Dose	Route	Cycle
Olaparib tablets	300mg twice daily*	PO	Continuous
*Total daily dose 600mg.			
If a patient misses a dose of olaparib, they should take their next normal dose at its scheduled time.			
Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets may be taken without regard to meals.			
Olaparib tablets are available as 100 mg and 150 mg tablets.			

ELIGIBILITY:

- Indications as above
- BRCA 1/2 mutation (germline and/or somatic) as demonstrated by an accurate and validated test method
- Adequate organ function

1L Maintenance treatment of BRCA-mutated advanced ovarian cancer:

- Platinum-responsive histologically confirmed high risk advanced (FIGO stage III-IV) BRCA mutated high grade serous or high-grade endometrioid ovarian cancer, primary peritoneal cancer or fallopian-tube cancer:
    - Platinum-responsive defined as partial or complete clinical response to platinum treatment,
    - Completed at least 4 cycles of first-line platinum chemotherapy and in radiologic (complete or partial) response, and
    - Last dose of platinum chemotherapy within 8 weeks of starting olaparib maintenance*
- Stage III or IV disease (patients may have upfront or interval debulking surgery)
    - *Where debulking surgery is required last dose of platinum chemotherapy should be within 12 weeks of starting olaparib maintenance
- ECOG 0-1
- Where patients who have commenced treatment with bevacizumab concomitant with chemotherapy are found to have BRCA 1/2mutation (germline or somatic) bevacizumab may be discontinued and treatment with olaparib maintenance commenced 4-8 weeks after the last dose of chemotherapy

Maintenance treatment of platinum-sensitive relapsed BRCA-mutated ovarian cancer:

- ECOG status 0-2
- Completed their previous platinum containing chemotherapy regimen in the previous 8 weeks
- Completed at least two courses of platinum-based chemotherapy
- The cancer is required to be platinum-sensitive (an objective response to the penultimate platinum-based regimen of more than six months) and the most recent regimen must have induced an objective response (either partial (PR) or complete response (CR))
- Patients' pre-treatment CA-125 value is within the upper limit of normal, or if greater, then a repeated level after seven days increased by less than 15% of the first measurement
- Life expectancy at least 16 weeks

Treatment of prostate cancer:

- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to olaparib, or any of the excipients.
- Hepatic impairment (bilirubin > 1.5 x ULN)
- Previous treatment with PARP inhibitor

Ovarian cancer indications:

- Breast-feeding during treatment and for 1 month after the last dose
- Pregnancy

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the breast cancer susceptibility
  - Information on BRCA testing for olaparib is available here
- FBC, renal and liver profile

Ovarian cancer indications:

- A pregnancy test should be performed on all premenopausal women prior to treatment

Regular tests:

- FBC, renal and liver profile every 4 weeks for the first 12 months and then as clinically indicated

Ovarian cancer indications:

- Consider regular pregnancy testing as indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Treatment may be interrupted to manage adverse reactions such as nausea, vomiting, diarrhoea, and anaemia and dose reduction can be considered (Table 1)

Table 1: Dose reduction levels of olaparib

Dose Level	Dose Recommendation	Total Daily Dose
Starting dose	300mg Twice Daily	600mg
Dose -1	250mg Twice Daily	500mg
Dose -2	200mg Twice Daily	400mg

Haematological:

Table 2: Recommended dose modification of olaparib in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1	And	≥100	100% of previous cycle's dose
<1	Or	<100	Delay until recovery then restart at a reduced dose level as per Table 1 above 4th occurrence: Cease olaparib
Febrile Neutropenia			Delay until recovery then restart at a reduced dose level as per Table 1 above 4th occurrence: Cease olaparib For grade 4 febrile neutropenia consider restarting olaparib at dose reduction of two dose levels

Renal and Hepatic Impairment:

Table 3: Recommended dose modification of olaparib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Cr Cl (ml/min)	**Dose**	**Impairment Level**	**Dose**
>50	300mg PO twice daily	**Mild/Child-Pugh A**	100% dose
31-50	200mg PO twice daily	**Moderate/Child-Pugh B**	100% dose
≤30	Not recommended*	**Severe/Child-Pugh C**	Not recommended 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			

Dose adjustments for co-administration with CYP3A inhibitors

- Concomitant use of strong and moderate CYP3A inhibitors is not recommended and alternative agents should be considered.
  - Examples of strong inhibitors: clarithromycin, itraconazole, ketoconazole, grapefruit juice.
  - Examples of moderate inhibitors: aprepitant, erythromycin, diltiazem, fluconazole, ciclosporin, ciprofloxacin.
- If a strong or moderate CYP3A inhibitor must be co-administered the recommended dose of olaparib is shown in Table 4 below.

Table 4: Recommended olaparib dose reduction when co-administered with strong or moderate CYP3A inhibitors

Class of CYP3A inhibitor	Dose	Total daily dose
Strong CYP3A inhibitor	100mg twice daily	200mg
Moderate CYP3A inhibitor	150mg twice daily	300mg

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate to high (**Refer to local policy).**

PREMEDICATIONS:

Consider the use of:

- Anti-emetics (**Refer to local policy).**
- Proton Pump Inhibitor (**Refer to local policy).**

OTHER SUPPORTIVE CARE:

- Women of childbearing potential must use effective contraception before, during therapy and for 6 months after receiving the last dose of olaparib. Due to the potential interaction of olaparib with hormonal contraception, an additional non-hormonal contraceptive method and regular pregnancy tests should be considered during treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **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:** Myelodysplastic syndrome/Acute Myeloid Leukaemia (MDS/AML) have been reported in a small number of patients who received olaparib alone or in combination with other anti-cancer drugs; the majority of cases have been fatal. The duration of therapy with olaparib in patients who developed MDS/AML varied from <6 months to >4 years. 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 has been reported in a small number of patients receiving olaparib, and some reports have been fatal. 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.
- **Folate deficiency:** Case reports of folate deficiency have been published. Physicians should monitor levels and treat accordingly. An international study to evaluate the serum folate levels in patients treated with olaparib is ongoing.

- **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.
- **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.

DRUG 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 other anticancer medicinal products.
- 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 as per Table 4 above.
- Olaparib co-administration with strong or moderate CYP3A inducers is not recommended. In the event that a patient is 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.
- 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 are combined with olaparib.
    - Appropriate clinical monitoring is recommended for patients receiving CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.
- Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp can also not be excluded. Therefore, olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes and transport protein. The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.
- In vitro, olaparib inhibits the efflux transporter P-gp, therefore it cannot be excluded that olaparib may cause clinically relevant drug interactions with substrates of P-gp.
    - 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 BRCP (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 of olaparib with vaccines or immunosuppressant agents has not been studied. Therefore, caution should be taken if these drugs are co-administered with olaparib and patients should be closely monitored.

- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Moore et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018; 379:2495-2505 SOLO1
2. Ledermann J, Harter P et al. Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer. NEJM 2012; 366 (15):1392-1392.
3. Pujade-Lauraine, Eric et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 1274–84
4. De Bono et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM. 2020; 382:2091-2102 available here https://www.nejm.org/doi/full/10.1056/NEJMoa1911440
5. Hussain et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. NEJM. 2020;383:2345-57 available here https://pubmed.ncbi.nlm.nih.gov/32955174/
6. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
7. Shammo JM, Usha L, Richardson KJ, et al. Olaparib-induced severe folate deficiency in women with relapsed ovarian cancer: first report and case series. J Clin Oncol.2018; 36(suppl):e17540.
8. Yohannan B et al. Severe folate deficiency anemia associated with the use of a PARP inhibitor (olaparib) in a patient with fallopian tube cancer. Case reports in Internal Medicine. 2019 Vol 1 No 1. https://doi.org/10.5430/crim.v6n1p1
9. A Study of Serum Folate Levels in Patients Treated With Olaparib. ClinicalTrials.gov NCT04024254 Accessed 07/11/2019. Last updated: 18/07/2019. Available at: https://clinicaltrials.gov/ct2/show/NCT04024254?term=folate&intr=Olaparib&draw=2&rank=1
10. FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Last updated Oct 2020. Accessed Nov 2020. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2
11. Lynparza® 100mg Film coated tablets. Summary of product characteristics. Last update: 07/12/2021. Accessed January 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	26/11/2020		Prof Maccon Keane
2	21/12/2021	Addition of new indication	Prof Maccon Keane
3	01/03/2023	Addition of new indication	Dr Richard Bambury

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.