Olaparib (Tablet) and Bevacizumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability.	C56 C48 C57	00746a 00746b 00746c	Olaparib: CDS 1/9/2023 Bevacizumab: Hospital

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 patients individual clinical circumstances.

Olaparib is administered 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.

Bevacizumab is administered once every 21 days until disease progression or unacceptable toxicity occurs or for a maximum of 15 months (including the periods in combination with chemotherapy and as maintenance).

Facilities to treat anaphylaxis MUST be present when the systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Bevacizumab	15mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[a]	Repeat every 21 days
Continuous	Olaparib tablets[b,c,d]	300mg twice daily[e]	PO		Continuous

[a] The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.
If the first infusion is well tolerated, the second infusion may be administered over 60 minutes.
If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance[i] here.
It should not be administered as an intravenous push or bolus.

[b] If a patient misses a dose of olaparib, they should take their next normal dose at its scheduled time.

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

[d] Olaparib tablets are available as 100 mg and 150 mg tablets.

[e] Total daily dose 600mg.

ELIGIBILITY:

- Indication as above
- Cancer histologically confirmed as (a) high-grade serous, (b) high-grade endometrioid or (c) other epithelial non-mucinous ovarian cancer in a patient with a gBRCAm
- Completed first-line treatment with platinum-taxane chemotherapy in combination with bevacizumab, demonstrating a response (no evidence of disease (NED), complete response (CR) or partial response (PR))
    - Completed ≥6 and ≤9 cycles of platinum-taxane chemotherapy and
    - Received a minimum of 3 cycles of bevacizumab in combination with the last 3 cycles of platinum-based chemotherapy (Patients with interval debulking surgery (IDS) should have received a minimum of 2 cycles of bevacizumab)
- Homologous recombinant deficient tumour (defined by either a BRCA 1/2 mutation and/or genomic instability) determined using a validated test method[1]
- ECOG 0-1
- Adequate organ and bone marrow function

EXCLUSIONS:

- Hypersensitivity to olaparib, bevacizumab, Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies or to any of the excipients.
- Previous treatment with PARP inhibitor, including olaparib
- Hepatic impairment (bilirubin > 1.5 x ULN)
- History of MDS/AML
- Major surgery within 4 weeks
- Pregnancy
- Breast feeding during treatment and for 1 month after the last dose

USE WITH CAUTION:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness

[1] The terminology used in the drug indication licensed by the European Medicines Agency is homologous recombination deficiency (HRD) positive which is synonymous with Homologous Recombination Deficient (HR deficient).
Homologous Recombinant Proficient (HR proficient) therefore indicates that the tumour is homologous recombination deficiency (HRD) negative

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- A pregnancy test should be performed on all premenopausal women prior to treatment
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam
- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline
- INR if clinically indicated*

Regular tests:

- FBC, renal and liver profile every 3 weeks for the first 12 months and then as clinically indicated
- Consider regular pregnancy testing as indicated
- Dipstick urinalysis for protein
- Blood pressure prior to each cycle and post treatment
- INR if clinically indicated*

*For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.

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
- Olaparib:
  - 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

- Bevacizumab:
  - Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 4 and Table 5)

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 and bevacizumab in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Olaparib	**Cr Cl (ml/min)**	**Dose**	**Impairment level**	**Dose**
	>50	300mg PO twice daily	**Mild/Child-Pugh A**	100% dose
	30-50	200mg PO twice daily	**Moderate/Child-Pugh B**	100% dose
	<30	Consider 50% of the dose.	**Severe/Child-Pugh C**	Consider 50% of the original dose.
	Haemodialysis	Consider 50% of the original dose.		
Bevacizumab	No need for dose adjustment is expected. Haemodialysis: no need for dose adjustment is expected.		No need for dose adjustment is expected.	

Management of adverse events:

Proteinurea:

Table 4: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	Action
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below.
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection.
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour.
greater than 4	Discontinue Therapy

Table 5: Dose modification of bevacizumab for adverse events

Adverse reactions		Recommended dose modification
Hypertension	Uncontrolled * or symptomatic hypertension on Day 1	Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication
	Grade 2-3 hypertension	Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled
	Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
Grade 4 Proteinuria		Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula		Discontinue bevacizumab
Grade 4 Thromboembolic events		Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3		Discontinue bevacizumab
Gastrointestinal Perforation		Discontinue bevacizumab
*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication		

Dose adjustments of olaparib 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 6 below

Table 6: 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:

Olaparib: Moderate to high (**Refer to local policy)**
Bevacizumab: Minimal **(Refer to local policy)**

PREMEDICATIONS:

Olaparib:
Consider the use of:
- Anti-emetics (**Refer to local policy)**
- Proton Pump Inhibitor (**Refer to local policy)**

Bevacizumab:
- Not usually required unless the patient has had a previous hypersensitivity

OTHER SUPPORTIVE CARE:

Olaparib:
- Women of childbearing potential must use effective contraception before, during therapy and for 1 month 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.

Bevacizumab:
- Anti-diarrhoeal treatment may be required **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Olaparib:
- **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.
- **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.
- **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. (3)

Bevacizumab:

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Wound healing complications:** Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical

wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
    - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
    - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
    - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have bevacizumab discontinued.
    - It should be permanently discontinued if the patient develops hypertensive crisis or hypertensive encephalopathy.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.
- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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 6 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.

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Version	Date	Amendment	Approved By
1	1/9/2023		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The rapid infusion is an unlicensed means of administration of bevacizumab for the indications described above, in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.