Olaparib (Tablet) and Bevacizumab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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 01/09/2023 Bevacizumab: N/A

*This is for post 2012 indications only

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 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 90 minutes[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] Available on the NCCP website .

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 commonly available as 100 mg and 150 mg tablets.

[e] Total daily dose 600mg.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

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
- Major surgery within 4 weeks
- Pregnancy
- Breastfeeding 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

[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**

- History of MDS/AML
- 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
- Surgical procedure or complications that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation

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	**CrCl (mL/min)**	**Dose**	**Impairment level**	**Dose**
	>50	300mg PO twice daily	**Mild/Child-Pugh A**	No dose adjustment is needed

	30-50	200mg PO twice daily	**Moderate/Child-Pugh B**	No dose adjustment is needed
	<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.	
Renal and hepatic dose modifications from Giraud et al 2023				

Management of adverse events:

Proteinuria:

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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

Olaparib: Moderate to high (**Refer to local policy).**

Bevacizumab: Minimal **(Refer to local policy).**

For information:

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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 two forms of reliable contraception before starting treatment, during therapy and at least 6 months after receiving the last dose. 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

Bevacizumab:

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

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Ray-Coquard I et al. PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019 Dec 19; 381(25):2416-2428. doi: 10.1056/NEJMoa1911361. PMID: 31851799.
2. 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
3. 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
4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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

6. Olaparib (Lynparza®) 100mg film-coated tablets. Summary of Product Characteristics. Accessed September 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf
7. Bevacizumab (Avastin®) Summary of Product Characteristics.Accessed September 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/09/2023		Prof Maccon Keane
2	09/12/2024	Reviewed. Updated exclusions and cautions section. Updated wording in other supportive care section. Updated emetogenic potential section to add standard wording. Updated regimen in line with NCCP standardisation.	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.