Bevacizumab 10mg/kg and PACLitaxel 80mg/m^2 (Day 1, 8, 15 and 22) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.	C56 C57 C48	00769a	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.

Bevacizumab is administered on Days 1 and 15 and PACLitaxel is administered on Days 1, 8, 15 and 22 of a 28 day cycle until disease progression or unacceptable toxicity occurs.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 15	Bevacizumab	10mg/kg	IV infusion	100mL NaCl 0.9% over 90 minutes[a]	Every 28 days
1, 8, 15, 22	PACLitaxel[b]	80mg/m^2	IV infusion	250mL NaCl 0.9% over 1 hour	Every 28 days

[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 here
It should not be administered as an intravenous push or bolus.

[b] PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22µm filter with a microporous membrane. PACLitaxel should be diluted to a concentration of 0.3-1.2mg/mL.

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

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to bevacizumab, PACLitaxel or to any of the excipients
- Baseline neutrophil count < $1.5x10^9$ cells/L
- Severe hepatic impairment
- Pregnancy
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies

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
- 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
- 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*

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

Regular tests:

- FBC (including Day 8 FBC), renal and liver profile
- 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
- 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 1: Recommended dose modification for PACLitaxel for haematological toxicity

ANC ($x10^9$/L)		Platelets	Dose	Dose after neutropenic sepsis
≥ 1.5	and	> 90	80mg/m^2	65mg/m^2
*1-1.49	or	70-90	65mg/m^2	50mg/m^2
< 1	or	< 70	Delay and reduce next dose to 65mg/m^2 or add G-CSF	Delay
Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks should discontinue treatment.				

*** If ANC 1 to less than 1.5 and patient fit and well can consider full dose of 80 mg/m^2 at discretion of prescribing Consultant**

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for bevacizumab and PACLitaxel in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
Bevacizumab[a]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected	No need for dose adjustment is expected			
PACLitaxel[b]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected	**ALT**		**Total Bilirubin**	**Dose**
		< 10 x ULN	and	≤ 1.25 x ULN	No dose reduction
		< 10 x ULN	and	1.26-2 x ULN	75% of original dose
		< 10 x ULN	and	2.01-5 x ULN	50% of original dose
		≥ 10 x ULN	or	> 5 x ULN	Contraindicated

[a] Bevacizumab (renal and hepatic - Giraud et al 2023);
[b] PACLitaxel (renal and hepatic – Giraud et al 2023)

Management of adverse events:

Table 3: Recommended dose modification of PACLitaxel for Adverse Events

Adverse reactions	Dose
Grade 2 motor or sensory neuropathy	Decrease dose by 10mg/m^2
All other grade 2 non-haematological toxicity	Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m$^{2.}$
≥ Grade 3 reaction	Discontinue
Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment	

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/24hour)	**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 modifications 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		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

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

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

PREMEDICATIONS:

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

PACLitaxel:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
  - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
  - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 6 outlines suggested premedications prior to treatment with PACLitaxel.

Table 6: Suggested premedications prior to treatment with PACLitaxel

Day of treatment	Drug	Dose	Administration prior to PACLitaxel
Day 1	DexAMETHasone[a]	8mg IV	30 minutes
Day 1	Chlorphenamine	10mg IV	30 minutes
Day 1	Famotidine	20mg IV	30 minutes
Day 8[b] and thereafter	DexAMETHasone[a]	None	
Day 8 and thereafter	Chlorphenamine	10mg IV	30 minutes
Day 8 and thereafter	Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hour and 6 hour prior to re-challenge with PACLitaxel according to consultant guidance.			
[b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance.			
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.			

OTHER SUPPORTIVE CARE:

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

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

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. Pujade-Lauraine, E, Hilpert, F et al. Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open- Label Randomized Phase III Trial. J Clin Oncol. 2014;32:(13) 1302-1308.
2. 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/
3. 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
4. Bevacizumab (Avastin®) Summary of product characteristics. Last updated March 2023. Accessed February 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf
5. PACLitaxel Summary of Product Characteristics. Last updated September 2022. Accessed February 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-050-001_21092022103217.pdf

Version	Date	Amendment	Approved By
1	14/11/2022		Prof. Maccon Keane
2	05/06/2024	Reviewed. Updated Bevacizumab rapid rate guidance in line with NCCP standardisation. Updated cautions section. Updated renal and hepatic information in line with Giraud et al, 2023. Updated Table 5: dose modifications of bevacizumab for adverse events. Updated premedications section. Updated in line with NCCP standardization.	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.'