Bevacizumab 7.5mg/kg, CARBOplatin (AUC5) and PACLitaxel 175mg/m^2 Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Bevacizumab in combination with CARBOplatin and PACLitaxel is indicated as first line post -surgical treatment in FIGO stage III after surgery with residual disease ≥ 1cm or FIGO stage IV:		00620a	Bevacizumab: Hospital PACLitaxel: Hospital CARBOplatin: Hospital
Epithelial ovarian	C56		
Fallopian tube	C57		
Primary peritoneal cancer	C48		

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.

Bevacizumab, CARBOplatin and PACLitaxel are administered on day 1 of a 21 day cycle for up to 6 cycles followed by continued use of bevacizumab as a single agent for a maximum of 18 doses in total of bevacizumab or until disease progression or unacceptable toxicity, whichever occurs earlier.

Note: Treatment with bevacizumab should be omitted at cycle 1 to avoid delayed wound healing if chemotherapy is started within 4 weeks of surgery

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered

Cycle 1-6

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	PACLitaxel	175mg/m^2	IV infusion	500ml 0.9% NaCl over 3 hours[a,b]	21 days
2	1	CARBOplatin	AUC 5[c]	IV infusion	500ml glucose 5% over 60 min	21 days
3	1	Bevacizumab	7.5mg/kg	IV infusion	100ml 0.9% NaCl over 90 mins[d,e]	21 days
[a]PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.						
[b]PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.						
[C]CARBOplatin at a dose of AUC 6 may be considered in patients with good performance status where the Cockcroft and Gault equation is used to estimate Creatinine clearance, Where GFR is measured using an isotope study or estimated with the Wright equation, the dose should be AUC 5.						
[d]Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.						
[e]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. It should not be administered as an intravenous push or bolus						

Cycle 7 onwards (Maximum of 18 doses in total)

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Bevacizumab	7.5mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[a,b]	Repeat every 21 days
[a]Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.					
[b]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. It should not be administered as an intravenous push or bolus					

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR** may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min. (3)
- For obese patients and those with a low serum creatinine due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.
    - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered (4).
    - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 63 micromol/L or a steady pre-operative creatinine value may be considered (5)
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method (6). The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

GFR (ml/min) = S x (140 - age in years) x wt (kg)

serum creatinine (micromol/L)

S= 1.04 for females

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal and hepatic function

USE WITH CAUTION:

- Bleeding/clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- 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

EXCLUSIONS:

- Hypersensitivity to CARBOplatin*, PACLitaxel, bevacizumab or any of the excipients
- Pregnancy or lactation
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Severe hepatic impairment (PACLitaxel)
- Cerebrovascular disease (eg TIA, CVA or cerebral haemorrhage within 6 months prior to treatment)
- Cardiovascular disease eg MI within 6 months prior to treatment, poorly controlled arrhythmia, congestive cardiac failure >/= Class 2
- Baseline neutrophil count < 1.5 x 10^9 cells/L

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision (9).

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Audiometry if clinically indicated
- Dipstick urinalysis for protein
- Blood pressure measurement
- Cardiac assessment including history, physical exam and baseline ECG.
    - ECHO should be considered in patients who have a history of cardiovascular disease, prior treatment with an anthracycline or other cardiotoxic drug or prior chest wall radiation.

Regular tests (prior to each cycle):

- FBC with differential, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure (including post treatment).

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 (See Table 3 and 4).
- Dose modifications for PACLitaxel and CARBOplatin can be managed by the dose reduction table for haematological and adverse events.

Table 1: Suggested Dose Reductions for Toxicity[a]

Drug	Dose level	Dose level -1	Dose level -2	Dose level -3
PACLitaxel	175mg/m^2	135mg/m^2	[b]110 mg/m^2	Discontinue
CARBOplatin	AUC 6	AUC 5	AUC 4	Discontinue
	AUC 5	AUC 4	AUC 3.5	Discontinue
[a]For dose modifications for hepatic impairment see Table 3				
[b]If clinically appropriate rather than discontinuation				

Haematological:

Table 2: Dose Modifications for Haematological Toxicity*

ANC (x 10^9/L) On Treatment Day	
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery. Consider using prophylactic GSCF (preferred) or reducing PACLitaxel and CARBOplatin by one dose level for subsequent cycles
Febrile neutropenia	Delay treatment until recovery. Use prophylactic GCSF on subsequent cycles and consider reducing PACLitaxel and CARBOplatin by one dose level for subsequent cycles
Platelets (x 10^9/L) on treatment day	
50 to < 100	Delay treatment until recovery. Consider reducing PACLitaxel and CARBOplatin by one dose level for subsequent cycles; reduction is mandatory if recovery is > 7 days.
Platelets (x 10^9/L) at any stage in cycle	
50 to <100	Delay treatment until recovery.
<50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by one dose level for subsequent cycles
*For some patients, especially ECOG 2, treatment thresholds may be higher If a patient experiences significant myelosuppression, consideration should be given as to whether GFR is being over-estimated	

Renal and Hepatic Impairment:

Table 3: Dose Modifications in Renal and Hepatic Impairment

Drug	Renal Impairment	Hepatic Impairment			
CARBOplatin	See note below[a]	No dose modification required			
PACLitaxel	No dose modification required	**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
		< 10xULN	And	≤ 1.25xULN	175mg/m^2
		< 10xULN	and	1.26-2xULN	135mg/m^2
		< 10xULN	and	2.01-5xULN	90mg/m^2
		≥ 10xULN	and/or	> 5xULN	Not recommended
Bevacizumab	No studies have been performed in patients with renal impairment.	No studies have been performed in patients with hepatic impairment.			

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae, taking care this does result in a CARBOplatin dose reduction.

Management of Specific Adverse Events:

Table 4: Dose Modifications for Adverse Events

Adverse reactions		Recommended dose modification
Motor or sensory neuropathy	Grade 2 Grade ≥ 3	Reduce PACLitaxel by 1 dose level. If persists, reduce PACLitaxel by an additional dose level (see table) Omit PACLitaxel
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		

Table 5: Dose modifications of bevacizumab for proteinuria

≥2+ proteinuria (dipstick)	24 hour urine collection for total protein
≥2+ proteinuria (dipstick) and 24 hour proteinuria ≤ 2g	Continue with normal dose.
≥2+ proteinuria (dipstick) and 24 hour proteinuria > 2g	Withhold treatment until proteinuria < 2g at discretion of prescribing consultant. Re-check 24 hour urine protein every 2-4 weeks or as clinically indicated.
Nephrotic syndrome	Discontinue bevacizumab.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to PACLitaxel treatment.
- The H_2 antagonist, raNITIdine, 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 ranitidine 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 use of alternative H_2 antagonists such as IV famotidine (unlicensed) or where not available, alternate PO H_2 antagonists **(refer to local policy).**

Table 6: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
Dexamethasone	20mg oral or IV[a,b]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes prior to PACLitaxel administration
Chlorphenamine	10mg IV	30 minutes prior to PACLitaxel administration
RaNITIdine[c]	50mg IV	30 minutes prior to PACLitaxel administration
[a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexamethasone to 12mg on the day of treatment.		
[c]or equivalent e.g. famotidine IV		

OTHER SUPPORTIVE CARE:

- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.
- Anti-diarrhoeal treatment may be required with Bevacizumab **(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.

- **Neutropenia:** This is the dose limiting toxicity. Fever or other evidence of infection must be assessed promptly and treated appropriately.

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) or any symptomatic hypertension that is not controlled with medication should have bevacizumab permanently discontinued.
- **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.

CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin. Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

PACLitaxel

- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare. Dose reduction or discontinuation may be necessary.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. **(Refer to local policy).**
- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended

DRUG INTERACTIONS:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary, monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	21/06/2021		Dr Dearbhaile O'Donnell

Comments and feedback welcome at oncologydrugs@cancercontrol.ie

[i] 'This is an unlicensed posology for the use of Avastin® in Ireland. Patient's 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" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.'