Bevacizumab 15mg/kg, PACLitaxel 175mg/m^2 and CISplatin 50mg/m^2 Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced metastatic or recurrent or metastatic cervical cancer, not amenable to curative surgery or radiation therapy	C53	00799a	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.

Bevacizumab, PACLitaxel and CISplatin are administered on day 1 of a 21 day cycle until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when SACT is administered.

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	CISplatin	50mg/m^2	IV infusion	1000ml NaCl 0.9% over 1 hour (Pre and Post hydration therapy required)[c]	21 days
3	1	Bevacizumab	15mg/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]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload

[d]Flush line with NaCl 0.9% pre and post bevacizumab dose.

[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.
Alternatively, the unlicensed use of shorter infusion times[i] is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance here.
It should not be administered as an intravenous push or bolus.

ELIGIBILITY:

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

USE WITH CAUTION:

- Bleeding/clotting disorders
- History of significant venous thromboembolism
- Underlying condition or surgical procedure that could lead to increased risk of fistulation or perforation
- Clinically significant cardiovascular disease
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or pelvic region
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)

EXCLUSIONS:

- Hypersensitivity to bevacizumab, PACLitaxel, CISplatin or any of the excipients
- Pregnancy or lactation
- Major surgery within 4 weeks
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Baseline neutrophil count < 1.5 x 10^9 cells/L
- Severe hepatic impairment (PACLitaxel)
- Significant hearing impairment/tinnitus

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- 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.
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

Regular tests:

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure (including 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 (See tables 3 and 4).
- Dose modifications for PACLitaxel and CISplatin can be managed by the dose reduction table for haematological and adverse events.

Haematological:

Table 1: Dose modification of PACLitaxel and CISplatin in haematological toxicity

ANC ($x10^9$/L)	
0.5 to < 1.0	Delay treatment until recovery
<0.5	Delay treatment until recovery and consider reducing PACLitaxel and CISplatin by 25% for subsequent cycles
Febrile neutropenia	Delay treatment until recovery and consider reducing PACLitaxel and CISplatin by 25% for subsequent cycles
Platelets $x10^9$/L (pre-treatment blood test)	
75 to <100	Clinician decision – continue if patient is clinically well
50 to <75	Delay treatment until recovery
<50	Delay treatment until recovery and consider reducing PACLitaxel and CISplatin by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modification of in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modification required.			
	≥60	100%				
	50-59	75%				
	40-49	50%				
	<40	Not recommended. Consider carboplatin				
	Haemodialysis	50% dose may be considered				
PACLitaxel	No dose modification required		**ALT**		**Total bilirubin**	**Dose of PACLitaxel**
			< 10 x ULN	and	≤ 1.25 x ULN	175mg/m^2
			< 10 x ULN	and	1.26-2 x ULN	135mg/m^2
			< 10 x ULN	and	2.01-5 x ULN	90mg/m^2
			≥ 10 x ULN	and/or	> 5 x ULN	Not recommended
Bevacizumab	No studies have been performed in patients with renal impairment.		No studies have been performed in patients with hepatic impairment.			

Management of adverse events:

Table 3: Dose Modifications for Adverse Events

Adverse reactions		Recommended dose modification
Motor or sensory neuropathy	Grade 2 (which is present at start of next cycle)	Withhold paclitaxel and cisplatin until toxicity has resolved to Grade 1 or less and reduce the dose of paclitaxel and cisplatin by 25% for subsequent cycles. If delay is more than three weeks or recurrence of neuropathy, cease paclitaxel and Cisplatin
	Grade ≥ 3	Cease paclitaxel and cisplatin
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 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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS:

- 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 5 outlines suggested premedications prior to treatment with PACLitaxel

Table 5: 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
Chlorphenamine	10mg IV	30 minutes
Famotidine[c]	20mg IV	30 minutes
[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]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.		

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)**
- Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above).**

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.

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

CISplatin

- Renal toxicity is common with CISplatin. Encourage oral hydration.
- Ototoxicity and sensory neural damage should be assessed by history prior to each cycle**.**

DRUG INTERACTIONS:

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

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Version	Date	Amendment	Approved By
1	10/03/2023		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