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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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	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 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 chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 15	Bevacizumab	10mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[1]	Every 28 days
1, 8, 15, 22	PACLitaxel[2]	80mg/m^2	IV infusion	250ml 0.9% sodium chloride over 1hr	Every 28 days

[1] 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.
Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

[2] 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.

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:

Use with caution in patients with:

- 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

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*

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	No studies have been performed in patients with renal impairment.	No studies have been performed in patients with hepatic impairment.			
PACLitaxel	No recommended dose modifications in renal impairment	**ALT**		**Total Bilirubin**	**Dose**
		< 10 x ULN	and	≤ 1.25 x ULN	80mg/m^2
		< 10 x ULN	and	1.26-2 x ULN	60mg/m^2
		< 10 x ULN	and	2.01-5 x ULN	40mg/m^2
		≥ 10 x ULN	and/or	> 5 x ULN	Not recommended

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/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 modifications of bevacizumab for adverse events

Adverse reactions	Recommended dose modification
Hypertension: Uncontrolled or symptomatic hypertension on Day 1 *Grade 4 hypertension or persisting grade 3 hypertension	Withhold bevacizumab treatment, start antihypertensive therapy or adjust pre-existing medication 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

*National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3)

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

➢ The following table should be used in regimens where PACLitaxel is given on a **weekly** basis.

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 hr and 6 hr 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 / REGIMEN SPECIFIC COMPLICATIONS:

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

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.

PACLitaxel

- **Hypersensitivity:** 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.
- **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated **(Refer to local policy).**
- **Neutropenia:** This is the dose limiting toxicity. Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare.
- **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.
- **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:

- The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.
- No interaction studies have been performed between EGFR antibodies and bevacizumab. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy,

is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.
- Concurrent use of bevacizumab and sunitinib can increase the risk of microangiopathic haemolytic anaemia (MAHA).
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	14/11/2022		Prof. Maccon Keane

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