Regimen Monograph

A - Regimen Name

CRBPPACL+BEVA Regimen

PACLitaxel-CARBOplatin-Bevacizumab

Disease Site

Gynecologic - Ovary
epithelial ovarian, fallopian tube, or primary peritoneal cancer

Intent

Palliative
Curative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients with a high risk of relapse (stage III sub-optimally debulked*, stage III unresectable** or stage IV patients) and an ECOG performance status of 0-2.

Bevacizumab is not funded for neoadjuvant use; it should only be initiated after debulking surgery. See NDFP eligibility form for detailed funding criteria.

*sub-optimally debulked is defined as patients who have > 1 cm residual disease after debulking surgery

**only if initially deemed unresectable and cannot be optimally debulked after neoadjuvant chemotherapy

Recommendation as an evidence-informed regimen was based on a phase III study that demonstrated an improvement in progression-free and overall survival in high risk patients.

Supplementary Public Funding	**bevacizumab** New Drug Funding Program (Bevacizumab (Biosimilar) with Paclitaxel and Carboplatin - Front-line Treatment (Previously Untreated) Ovarian, Fallopian Tube, and Primary Peritoneal Cancer)

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B - Drug Regimen

Different bevacizumab products are **not interchangeable**.

PACLitaxel	175 mg /m²	IV over 3 hours	Day 1
followed by:			
CARBOplatin	AUC 4 to 6*	IV	Day 1

*Clinical trials used AUC 6. See section E for dose modifications for toxicity, age or other characteristics. Adjust Carboplatin dose to AUC target (using Calvert formula), as outlined in "Other Notes" section.

Starting in cycle 2 (or subsequent cycles):

bevacizumab	7.5 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles of carboplatin/paclitaxel, 5 in combination with bevacizumab, followed by bevacizumab alone for up to 12 additional cycles or until disease progression or unacceptable toxicity, whichever occurs first.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)
Moderate (Carboplatin AUC < 5)

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Patients should be pretreated with a corticosteroid, an antihistamine and a H2-blocker 30 minutes before paclitaxel. For example:

• dexamethasone 20mg IV (or PO 12 and 6 hours before)

• diphenhydramine 50mg IV

• ranitidine 50mg IV

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are from product monographs and clinical trials and may be considered. Bevacizumab should not be initiated until hypertension is controlled and wound healing has occurred, dental evaluation has been performed and any major dental procedures completed. May consider hypersensitivity prophylaxis for patients who have had prior mild hypersensitivity reactions and who are continuing on treatment.

Dosage with toxicity

Do not start a new cycle until ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L.

Dose levels

Dose level	carboplatin	paclitaxel (mg/m^2)	bevacizumab (mg/kg)
0	AUC 6	175	7.5
-1	AUC 5	135	7.5
-2	AUC 4	110	7.5

Dose modifications for carboplatin and paclitaxel

Toxicity (counts x 10^9/L)	Carboplatin	Paclitaxel
ANC < 1.5 for > 7d, febrile neutropenia OR grade 4 neutropenia for ≥ 7d	No change	Consider adding G-CSF and continue current dose OR ↓ 1 dose level
Neutropenia as defined above AND platelets < 100 for > 7d, grade 4 thrombocytopenia OR thrombocytopenic bleeding	↓ 1 dose level	Consider adding G-CSF and continue current dose OR ↓ 1 dose level
ANC ≥ 1.5 but platelets < 100, isolated grade 4 thrombocytopenia OR thrombocytopenic bleeding	↓ 1 dose level	No change
Other grade 3 or 4 non-hematologic toxicity	Hold until ≤ grade 1, then ↓ 1 dose level	Hold until ≤ grade 1, then ↓ 1 dose level
Grade 2 or higher neuropathy	No change	Hold paclitaxel until ≤ grade 1*, then ↓ 1 dose level

* If delay of > 3 weeks, omit paclitaxel from subsequent cycles and continue carboplatin

Hypersensitivity reactions

For patients at risk of hypersensitivity to carboplatin (cycle 7 onwards), consider premedication. For hypersensitivity reactions to paclitaxel and bevacizumab consider the following.

Reaction	Paclitaxel	Bevacizumab
Mild (e.g. mild flushing, rash, pruritus)	Possible to complete the infusion under close supervision	May hold the infusion. Give diphenhydramine and corticosteroid if indicated. Resume infusion at slower rate under close supervision.
Moderate (e.g. moderate rash, flushing, mild dyspnea, chest discomfort,	Stop the infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125	Hold the infusion. Give diphenhydramine and corticosteroid, or other

mild hypotension)	mg IV. Once symptoms have resolved, resume infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.	supportive measures as indicated. Consider discontinuing bevacizumab. If re-challenge on a different treatment day, use slower infusion rate.
Severe (e.g. one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Stop the infusion and give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators as indicated. Discontinue. Do not re-challenge.	Stop the infusion and give diphenhydramine and corticosteroid. Use epinephrine or bronchodilators as indicated. Discontinue. Do not re-challenge.

Dosage with toxicity for bevacizumab

Dose reductions are not recommended. Bevacizumab should be held or discontinued based on toxicity.

(Continued on next page)

Bevacizumab action	**Toxicity**		
	Any grade	**Grade 3**	**Grade 4**
Hold:	Uncontrolled hypertension		
	Delayed wound healing		
	Proteinuria ≥ 2g/ 24 hours*		
	Surgery**		
Discontinue:		Hypertension (not controlled with medical management)	Hypertension
	Wound dehiscence, poor healing requiring medical intervention; Necrotizing fasciitis		
	Nephrotic syndrome; non- recovery of proteinuria ≥ 2g/24 hours		
	Severe hypersensitivity reaction		
	Tracheo-esophageal fistula, other non-GI fistulae		Any internal fistula
	GI Perforation or fistula		
	PRES/RPLS		
	Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)
	Symptomatic cardiac failure		
	Recurrent hemoptysis > 2.5 mL	Bleeding (any)	Bleeding (any)
	Intracranial bleeding		
* may restart when < 2g/24hrs ** for 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed			

Hepatic Impairment

Bilirubin		AST/ALT	paclitaxel	carboplatin	bevacizumab
2-4 x ULN	OR	2-4 x ULN	Reduce dose to 135mg/m^2	No change	No change
> 4 ULN	OR	> 4 x ULN	OMIT	No change	No change

Renal Impairment

Creatinine clearance (mL/min)	paclitaxel	carboplatin	bevacizumab
20-50	No dosage adjustment	Use Calvert formula (refer to other notes section)	No information found
<20		Discontinue	

Dosage in the elderly:

Use with caution; patients > 65 years old have an increased risk of arterial thrombotic events as well as myelosuppression, fatigue, proteinuria, hypertension, dizziness, dysphonia, anorexia and GI effects. The lower dose range for carboplatin may be better tolerated in these patients.

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F - Adverse Effects

Refer to PACLitaxel, CARBOplatin, bevacizumab drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia • Peripheral neuropathy (may be severe) • Musculoskeletal pain • Myelosuppression +/- infection, bleeding (may be severe) • Nausea, vomiting	• Hypertension (may be severe) • Hypersensitivity • Ovarian failure • Proteinuria (may be severe) • Increased LFTs (may be severe) • Diarrhea (may be severe) • Nephrotoxicity (may be severe)	• Edema • Insomnia • Mucositis • Fatigue • Hearing impaired • Anorexia • ECG changes • Cardiotoxicity • Constipation • Dysgeusia • Dysphonia • Abdominal pain • Headache • Rash (may be severe) • Eye disorders • Hand-foot syndrome • Abnormal electrolytes • Venous thromboembolism (may be severe) • Cough, dyspnea	• Arterial thromboembolism • Delayed wound healing • Cystoid macular edema • GI obstruction, perforation • Fistulas • Hemolytic uremic syndrome • Necrotizing fasciitis • Osteonecrosis of the jaw • Pancreatitis • Pneumonitis • PRES • Pulmonary hypertension • Thrombotic microangiopathy

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G - Interactions

Refer to PACLitaxel, CARBOplatin, bevacizumab drug monograph(s) for additional details

- Use with caution with bisphosphonates and anti-angiogenic drugs given increased risk of ONJ

- Monitor closely with aminoglycosides and other nephrotoxic drugs, including diuretics
- Monitor closely with phenytoin; phenytoin dosage adjustment may be required
- Monitor INR in patients receiving warfarin; warfarin dosage adjustment may be required.
- Concurrent use with radiation may increase the risk of radiation pneumonitis
- Caution and monitor with CYP3A4 inducers (e.g. phenytoin, St. John's wort) and inhibitors (e.g. azole antifungals, macrolide antibiotics)
- Caution and monitor with CYP2C8 inducers (e.g. phenobarbital) and inhibitors (e.g. gemfibrozil, monteleukast)

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H - Drug Administration and Special Precautions

Refer to PACLitaxel, CARBOplatin, bevacizumab drug monograph(s) for additional details.

Different bevacizumab products are **not interchangeable**.

Administration:

PACLitaxel

- Use non-PVC equipment, including 0.22 micron in-line filter, in order to minimize patients' exposure to DEHP leaching from PVC bags or sets; infuse over 3 hours.
- Dilute in 500-1000 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided.
- Precipitation may rarely occur with infusions longer than 3 hours.

CARBOplatin

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light

Bevacizumab

- Bevacizumab infusions should not be administered or mixed with Dextrose or Glucose solutions due to potential for drug degradation.
- Mix in 100 mL bag NS. (Dilution should be 1.4 -16.5 mg/mL).
- Do not shake. Should not be mixed or diluted with other drugs.
- Compatible with PVC or polyolefin bags.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS
- Infused over 90 minutes as loading dose, if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes as maintenance dose
- Refrigerate unopened vials and protect from light; do not freeze.

Contraindications:

- Patients with known hypersensitivity to Chinese hamster ovary cell product, to other recombinant human or humanized antibodies, platinum-containing compounds, severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with untreated CNS metastases, recurrent hemoptysis (>2.5ml) or serious hemorrhage

Other Warnings/Precautions:

- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients with a history of arterial thromboembolism or significant cardiovascular disease or cardiac failure
- Congestive heart failure (including LVEF decrease) has been reported in patients who have received other chemotherapy agents, especially anthracyclines
- Patients with coagulopathies (congenital, acquired or therapeutic)
- Bevacizumab should not be initiated for at least 28 days following major surgery or until wound healing has occurred; hold for 28 days prior to major elective surgery
- The safety and efficacy of concurrent radiotherapy and bevacizumab has not been established
- Use with caution in patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis
- Use with caution in patients with, and those at risk of renal impairment
- Paclitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.

Pregnancy and Lactation:

- This regimen not recommended for use in pregnancy. Cases of fetal abnormalities have been reported with bevacizumab. Adequate contraception (including at least 2 contraceptive methods) should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle

- ECG monitoring if experiences arrhythmia
- Liver and renal function tests; baseline and before each cycle
- Monitor blood pressure during paclitaxel infusion and every 2-3 weeks during bevacizumab therapy and more frequently in patients who develop hypertension.
- Dental evaluation; baseline and as clinically indicated
- Baseline and regular dipstick urinalysis; 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick
- Clinical toxicity assessment (including hypersensitivity, musculoskeletal, perforation, fistula, GI symptoms, hemorrhage, infection, ONJ, thromboembolism, myelosuppression, arrhythmia, wound healing, hypertension, neurologic and cardiac effects); at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Cardiac function tests (Echo, RNA and/or MUGA scans) especially in patients who are close to the lifetime cumulative dose of anthracyclines/anthracenediones; baseline and as clinically indicated
- INR for patients receiving warfarin; baseline and regular

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J - Administrative Information

Approximate Patient Visit	First cycle: 7.5 hours; Second cycle: 7 hours, Subsequent cycles: 6.5 hours
Pharmacy Workload (average time per visit)	36.896 minutes
Nursing Workload (average time per visit)	69.833 minutes

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K - References

Bevacizumab, carboplatin and paclitaxel drug monographs, Cancer Care Ontario.

Perren TJ, Swart AM, Pfisterer J, et al; ICON7 Investigators. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2484-96.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Recurrent Epithelial Ovarian Cancer
- Neoadjuvant and Adjuvant Systemic therapy for Newly Diagnosed Stage II, III, or IV Epithelial Ovary, Fallopian Tube, or Primary Peritoneal Carcinoma

March 2021 Added PEBC guideline link

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L - Other Notes

Calvert Formula: (area under the curve method)

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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