Regimen Monograph

A - Regimen Name

CRBPPACL+BEVA Regimen

PACLitaxel-CARBOplatin-Bevacizumab

Disease Site	Gynecologic - Cervix
Intent	Palliative
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 the treatment of patients with metastatic, recurrent or persistent cervical cancer of all histologic subtypes (except small cell), who have an ECOG performance status of 0 or 1 (see NDFP for detailed funding criteria). Carboplatin combination treatment is a reasonable alternative for patients who cannot receive cisplatin.
Supplementary Public Funding	**bevacizumab** New Drug Funding Program (Bevacizumab (Biosimilar) - Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix)

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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

Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in "Other Notes" section.

bevacizumab	15 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression, no evidence of further response, or unacceptable toxicity.

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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.

Paclitaxel: Patients should be pretreated with a corticosteroid as well as an antihistamine and a H2 blocker.

For example: dexamethasone 20mg PO 12 & 6 hours OR 20mg IV 30 minutes before paclitaxel, diphenhydramine 50mg IV 30 minutes before paclitaxel and ranitidine 50mg IV 30 minutes before paclitaxel.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. 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 (see section D for examples) for patients who have had prior mild hypersensitivity reactions to bevacizumab and who are continuing on bevacizumab-only 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	15
-1	AUC 5	135	15
-2	AUC 4	110	15

Hematologic toxicity

Toxicity	Carboplatin	Paclitaxel	Bevacizumab
Febrile neutropenia or Grade 4 neutropenia for > 7d	No change	↓ 1 dose level, consider adding G-CSF for subsequent cycles if recurs*	No change
Grade 4 thrombocytopenia or thrombocytopenic bleeding	No change	↓ 1 dose level	Hold

*If recurs despite addition of G-CSF, reduce a second dose level

Hypersensitivity reactions

For patients at risk of hypersensitivity to carboplatin (cycle 7 onwards), consider premedication (see section D for examples) if paclitaxel is held for toxicity.

The following are suggestions for hypersensitivity with paclitaxel and bevacizumab.

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, mild hypotension)	Stop the infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 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.	Hold the infusion. Give diphenhydramine and corticosteroid, or other 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.

Non-hematologic toxicities

Any grade	**Grade 3**	**Grade 4**	**Bevacizumab action**	**Paclitaxel/ carboplatin action**
Uncontrollable hypertension*			Hold*	Consider hold or discontinue
Delayed wound healing; Surgery**				
Proteinuria ≥2g/24 hours***				

Wound dehiscence; Necrotizing fasciitis			Discontinue	Consider hold or discontinue
Tracheo-esophageal fistula, other non-GI fistulae; GI perforation		Any internal fistula		
Nephrotic syndrome; non recovery of proteinuria ≥2g/24 hours	Hypertension (not controlled with medical management)	Hypertension		
Severe Hypersensitivity				
PRES/RPLS				
Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)		
Symptomatic cardiac failure				
Recurrent hemoptysis > 2.5mL; Intracranial bleeding	Bleeding (any)	Bleeding (any)		
	Other non-hematologic	Other non-hematologic	No change	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 held for 3 weeks, discontinue bevacizumab and continue chemotherapy. If held 4 or more weeks, discontinue treatment.

**For 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed

***May restart when < 2g/24hrs

[#]If delay of > 3 weeks, omit paclitaxel from subsequent cycles and continue carboplatin

Hepatic Impairment

Bilirubin		AST/ALT	paclitaxel	carboplatin	bevacizumab
1-2 x ULN			no change	no change	no change
>2-3 x ULN	OR	2-5 x ULN	↓ 1 dose level	no change	no change
>3 x ULN	OR	> 5 x ULN	discontinue	no change	no change

Renal Impairment

Creatinine clearance (mL/min)	paclitaxel	carboplatin	bevacizumab
20-50	No dosage adjustment	Use Calvert or Chatelut 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, dysphonia and GI effects.

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F - Adverse Effects

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

Increased rates of thromboembolism and fistulas were reported in cervical cancer patients in clinical trials.

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Alopecia • Peripheral neuropathy (may be severe) • Musculoskeletal pain • Myelosuppression +/- infection, bleeding (may be severe) • Hemorrhage (may be severe) • Nausea, vomiting (may be severe) • Hypertension (may be severe) • Hypersensitivity (may be severe) • Ovarian failure • Proteinuria (may be severe) • Increased LFTs (may be severe) • Diarrhea (may be severe) • Nephrotoxicity (may be severe) • Edema • Insomnia, somnolence • Mucositis, dysguesia • Fatigue • Hearing impaired • Anorexia • Constipation • Headache • Cough, dyspnea (may be severe) • Rash (may be severe) • Eye disorders • Venous thromboembolism (may be severe) • Electrolyte abnormalities	• Arterial thromboembolism • Cardiotoxicity, arrhythmia • Pulmonary hypertension • GI perforation, obstruction • Fistula (GI and non-GI) • PRES, seizure • Osteonecrosis (jaw, other) • Pancreatitis • Thrombotic microangiopathy • Hemolytic uremic syndrome • Cystoid macular edema • Delayed wound healing • Necrotizing fasciitis • Secondary malignancy • Encephalopathy

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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, montelukast)

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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
- Patients with 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
- Patients with coagulopathies (congenital, acquired or therapeutic)
- Hypertension should be controlled prior to starting treatment
- 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
- Congestive heart failure (including LVEF decrease) has been reported in patients who have received other chemotherapy agents, especially anthracyclines.
- 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.

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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
- EKG monitoring if experiences arrhythmia
- Liver and renal function tests; baseline and before each cycle
- Dental evaluation; baseline

- Monitor blood pressure during paclitaxel infusion and every 2-3 weeks during bevacizumab therapy and more frequently in patients who develop hypertension.
- 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

Carboplatin, paclitaxel, bevacizumab drug monographs, Cancer Care Ontario.

Takano M, Kikuchi Y, Kita T, et al. Complete remission of metastatic and relapsed uterine cervical cancers using weekly administration of bevacizumab and paclitaxel/carboplatin. Onkologie. 2009 Oct;32(10):595-7.

Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014 Feb 20;370(8):734-43.

August 2019 added bevacizumab (biosimilar) NDFP form and non-interchangeability description

for bevacizumab

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L - Other Notes

Calvert Formula

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.

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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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