Regimen Monograph

A - Regimen Name

CRBPPACL Regimen

PACLitaxel-CARBOplatin

Disease Site	Gynecologic - Ovary
Intent	Adjuvant
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	First-line postoperative treatment for stage II-IV epithelial ovarian cancer, fallopian tube or primary peritoneal cancers

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B - Drug Regimen

PACLitaxel	175 mg /m²	IV	Day 1
CARBOplatin	AUC 5 to 6*	IV	Day 1

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

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

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

Also refer to CCO Antiemetic Recommendations.

Pre-medications (prophylaxis for infusion reaction):

Paclitaxel*:

- Dexamethasone 20 mg PO 12- and 6-hours OR Dexamethasone 20 mg IV 30 minutes pre-infusion†
- Diphenhydramine 25-50 mg IV/PO 30-60 minutes pre-infusion
- Ranitidine 50 mg IV OR Famotidine 20 mg IV 30-60 minutes pre-infusion

*Consider **discontinuing** pre-medications for paclitaxel if there was no IR in the first 2 doses.

†Oral and IV dexamethasone are both effective at reducing overall IR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern.

Carboplatin:

- There is insufficient evidence that routine prophylaxis with pre-medications reduce infusion reaction (IR) rates.
- Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists **may** reduce IR rates for some patients (e.g. gynecological patients with a platinum-free interval (PFI) > 12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal pre-medication regimen has been established.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Suggested Dose Levels for Paclitaxel:

Dose Level	Paclitaxel (mg/m^2)
0	175
-1	135
-2	110

Worst Toxicity (Counts x 10^9/L)	Carboplatin	Paclitaxel
ANC < 1.5 for > 7 days	Hold[1]; No change upon restart	Hold[1], then Consider adding G-CSF and continue current dose, if appropriate OR ↓ 1 dose level
ANC < 0.5 for ≥ 7 days or Febrile Neutropenia	Hold[1]; ↓ 1 AUC upon restart	Hold[1], then Consider adding G-CSF and continue current dose, if appropriate OR ↓ 1 dose level
Platelets < 25 or Thrombocytopenic bleeding	Hold[1]; ↓ 1 AUC upon restart	Hold[1]; ↓ 1 dose level upon restart
Grade 2 neuropathy	No change	Omit or consider ↓ 1 dose level
Grade 3 neuropathy	No change	Omit or ↓ 1 dose level

Other Grade 3 non-hematologic toxicity	Hold[1]; ↓ 1 AUC upon restart	Hold[1]; ↓ 1 dose level upon restart
Grade 4 non-hematologic toxicity	Discontinue	Discontinue
Any grade cystoid macular edema	No change	Discontinue

[1]Do not start new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and non-hematological toxicities have recovered to ≤ grade 2.

Management of Infusion-related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge	
	Carboplatin / Paclitaxel	**Carboplatin#**	**Paclitaxel**
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge. • May consider adding oral montelukast ± oral acetylsalicylic acid.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, consider replacing with a different taxane. Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider

		• Consider desensitization if therapy is necessary.	desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

#There is evidence that re-challenging with **cisplatin** after carboplatin reaction can be a viable option, however, exact cross reactivity between platinum agents is not known, but can be as high as 25%.

*Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist).

Hepatic Impairment

For paclitaxel, caution and dose reduction are advised in patients with moderate to severe hepatic impairment. Patients receiving paclitaxel with hepatic impairment may be at risk of toxicity, especially severe myelosuppression.

Suggested dose modifications are:

Bilirubin		**AST/ALT**	**PACLitaxel (% usual dose)**	**CARBOplatin (% usual dose)**
≤ 1.25 x ULN	AND	2 to 10 x ULN	75%	No change
1.26 to 2.5 x ULN	AND	< 10 x ULN	40%	
2.6 to 4 x ULN	AND	< 10 x ULN	25%	
> 4 x ULN	AND/OR	≥ 10 x ULN	Consider risk-benefit or Omit	

Renal Impairment

Creatinine Clearance (mL/min)	Paclitaxel	Carboplatin
20 - 50	No change	Use Calvert formula*
< 20		Discontinue

*Refer to "Other Notes" section.

Dosage in the Elderly

No adjustment required, but elderly patients are more at risk for severe toxicity. Caution should be exercised and dose reduction considered with carboplatin as elderly patients may have reduced renal function, more severe myelosuppression and neuropathy.

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F - Adverse Effects

Refer to PACLitaxel, CARBOplatin 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 (rarely permanent) • Peripheral neuropathy (may be severe) • Myelosuppression ± infection, bleeding (may be severe) • Musculoskeletal pain • Nausea, vomiting	• Hypersensitivity • Abnormal electrolytes • Nephrotoxicity (may be severe) • Fatigue	• Edema • Mucositis • Constipation • Diarrhea (may be severe) • ↑ LFTs • Hearing impairment • ECG changes	• Arrhythmia, cardiac failure • Arterial / venous thromboembolism • Rash • Radiation recall reaction • GI obstruction / perforation • Hemolytic uremic syndrome • Pancreatitis • Injection site reaction

			• Secondary malignancy • Autonomic, cranial neuropathy • Encephalopathy • Cystoid macular edema • Seizure • Pneumonitis • Visual disturbances

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G - Interactions

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

- Monitor INR in patients receiving warfarin; warfarin dosage adjustment may be required.
- Monitor closely with nephrotoxic and ototoxic drugs (ie. aminoglycosides) due to additive effects.
- Monitor closely with phenytoin; phenytoin dose adjustment may be required.
- Avoid if possible, or caution with radiation; may increase the risk of radiation pneumonitis.

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H - Drug Administration and Special Precautions

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

Administration

Paclitaxel:

- In order to minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets (with a 0.22 micron in-line filter).

- Dilute in 500-1000 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL and infuse over 3 hours.
- Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.
- 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.
- There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients with a history of severe hypersensitivity to platinum-containing compounds, paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with pre-existing, severe renal impairment
- Patients with severe myelosuppression or bleeding tumours

Warnings/Precautions

- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs
- 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.
- Avoid live vaccines. Reduced immunogenicity may occur with the use of inactivated vaccines.

Pregnancy/Lactation

- Carboplatin and paclitaxel are not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility Effects:
  - Carboplatin: Unknown
  - Paclitaxel: Yes

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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
- Liver function tests; baseline and before each cycle
- Renal function tests (including electrolytes); baseline and before each cycle
- Blood pressure and pulse; during paclitaxel infusion
- Opthalmology, if visual impairment; as clinically indicated
- Clinical assessment of thromboembolism, bleeding, GI effects, infection, musculoskeletal, ototoxicity, neurotoxicity, hypersensitivity and respiratory effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR; baseline and as clinically indicated
- Continuous cardiac monitoring; during subsequent infusions in patients who developed serious conduction abnormalities

- Cardiac function tests; baseline and as clinically indicated, especially in patients who are close to the lifetime cumulative dose of anthracyclines / anthracenediones

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J - Administrative Information

Approximate Patient Visit	5-6 hours
Pharmacy Workload (average time per visit)	30.383 minutes
Nursing Workload (average time per visit)	59.833 minutes

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K - References

Carboplatin and paclitaxel drug monographs, Cancer Care Ontario.

du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95:1320-30.

Kwon JS, Elit L, Finn M et al. A comparison of two prophylactic regimens for hypersensitivity recations to paclitaxel. Gynecol Oncol 2002 Mar; 84(3): 420-5.

Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-200.

The International Collaborative Ovarian Neoplasm (ICON) Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002; 360:505-15.

PEBC Advice Documents or Guidelines

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

June 2021 removed paclitaxel NDFP funding info

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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.

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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