Regimen Monograph

A - Regimen Name

CRBPPAC+ETOP(PO) Regimen

PACLitaxel-CARBOplatin-Etoposide (oral)

Disease Site	Unknown Primary
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 treatment of metastatic carcinoma of unknown primary. This regimen produced significantly higher myelosuppression but lower GI toxicity than GEMCIRIN in the phase III trial, although response rates, progression-free survival and 2-year survival were similar
Supplementary Public Funding	**etoposide** ODB - General Benefit (etoposide - oral capsules) (ODB Formulary)

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B - Drug Regimen

PACLitaxel	175 to 200 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.

etoposide	50 mg	PO	Days 1, 3, 5, 7, 9
etoposide	100 mg	PO	Days 2, 4, 6, 8, 10

(outpatient prescription in multiples of 50mg capsules)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles or until evidence of progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)
No routine prophylaxis for etoposide PO

Other Supportive Care:

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

- Dexamethasone: 20mg PO 12 & 6 hours before paclitaxel OR 20mg IV 30 minutes before paclitaxel
- Diphenhydramine: 50mg IV 30 minutes before paclitaxel
- Ranitidine: 50mg IV 30 minutes before paclitaxel

Also refer to CCO Antiemetic Recommendations.

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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 have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Day 1:

Worst Toxicity / Counts ($x10^9$/L) in previous cycle)		**Worst Toxicity / Counts ($x10^9$/L) in previous cycle**	**PACLitaxel (% previous dose)**	**CARBOplatin (% previous dose)**	**Etoposide**
Febrile neutropenia Or ANC < 0.5 for ≥ 5-7d	OR	Thrombocytopenic bleeding Or Platelets < 25	Hold*, then 75%	Hold*, then ↓ 1 AUC#	Give etoposide on days 1 to 8 only
Grade 3 neurotoxicity or related organ / non-hematologic			Hold*, then 75% if related	Hold*, then ↓ 1 AUC if related	Give etoposide on days 1 to 8 only, if related
Grade 4 neurotoxicity or related organ / non-hematologic; > 3 week delay due to toxicity			Discontinue	Discontinue	Discontinue

*Do not restart new cycle until toxicities have recovered to ≤ grade 1, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Day 8:

Counts (x 10^9/L)		Counts (x 10^9/L)	Etoposide
ANC < 1.5	Or	Platelets < 75	Omit doses for days 8 to 10

Paclitaxel - Hypersensitivity:

- **For mild symptoms** (e.g., mild flushing, rash, pruritus), attempt to complete the infusion under close supervision.
- **For moderate symptoms** (e.g., moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension),
  - Stop the paclitaxel infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV.
  - Once symptoms have resolved, resume paclitaxel 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.
- **For severe symptoms** (e.g., one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy),
  - Stop the paclitaxel infusion; give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators if indicated.
  - Do not rechallenge with paclitaxel.

Hepatic Impairment

Bilirubin		AST/ALT	PACLitaxel (% previous dose)	CARBOplatin (% previous dose)	etoposide (% previous dose)
1-2 x ULN			No change	No change	50%
>2-4 x ULN	or	2-4 x ULN	135 mg/m^2	No change	25%
>4 x ULN	or	>4 x ULN	50 mg/m^2 or OMIT	No change	Discontinue

Renal Impairment

Creatinine Clearance (mL/min)	Paclitaxel	Carboplatin (% previous dose)	Etoposide (% previous dose)
20 - 50	No change	Use Calvert Formula	75%
<20	No change	Discontinue	50% or Discontinue

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection, bleeding (may be severe) • Neuropathy (may be severe) • Alopecia • Diarrhea, mucositis • Edema • Fatigue • Nausea and vomiting • Hypersensitivity (may be severe) • Myalgia, arthralgia • Increase in LFTs (may be severe) • Nephrotoxicity, electrolyte abnormalities • Anorexia	• Arrhythmia, cardiotoxicity, acute MI • Arterial, venous thromboembolism • Pancreatitis, perforation, obstruction • Secondary malignancy • Pneumonitis • Rash • Hemolytic-uremic syndrome • Encephalopathy

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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; days 1 and 8
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular including electrolytes
- Blood pressure and pulse rate monitoring during paclitaxel infusion, cardiac monitoring with prior arrhythmia
- Clinical assessment of fever, infection, stomatitis, GI, bleeding, thromboembolism, musculoskeletal, neurologic (sensory), ototoxicity, hypersensitivity and flu-like symptoms

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

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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

Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. J Clin Oncol 2000;18(17):3101-7.

Greco FA, Rodriguez GI, Shaffer DW, et al. Carcinoma of unknown primary site: sequential treatment with paclitaxel/carboplatin/etoposide and gemcitabine/irinotecan: a Minnie Pearl Cancer Research Network phase II trial. Oncologist 2004;9(6):644-52.

Greco FA, Burris HA, Erland JB, et al. Carcinoma of unknown primary site: long term follow-up after treatment with paclitaxel, carboplatin, and etoposide. Cancer 2000;89(12):2655-60.

Hainsworth JD, Spigel DR, Clark BL, et al. Paclitaxel/carboplatin/etoposide versus gemcitabine/irinotecan in the first-line treatment of patients with carcinoma of unknown primary site: a randomized, phase III Sarah Cannon Oncology Research Consortium Trial. Cancer J. 2010 Jan-Feb;16(1):70-5.

Hainsworth JD, Spigel DR, Litchy S, Greco FA, et al. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network Study. J Clin Oncol 2006;24(22):3548-54.

Huebner G, Link H, Kohne CH, et al. German CUP Study Group. Paclitaxel and carboplatin vs gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: a randomised prospective phase II trial. Br J Cancer 2009;100(1):44-9.

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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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