Regimen Monograph

A - Regimen Name

PACL(W) Regimen

PACLitaxel (weekly)

Disease Site	Genitourinary - Bladder / Urothelial
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 second-line treatment of metastatic bladder cancer progressing on platinum-based chemotherapy.

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B - Drug Regimen

Option 1:

PACLitaxel	80 mg /m²	IV over 1 hour	Days 1, 8, 15 (3 weeks on, 1 week off)

Option 2:

PACLitaxel	80 mg /m²	IV over 1 hour	Days 1, 8, 15, 22 (weekly x 4)

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression, or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Pre-medications* (prophylaxis for infusion reaction):

To be given 30-60 minutes prior to paclitaxel infusion.

- Dexamethasone 10 mg IV, starting in cycle 1
- Diphenhydramine 25-50 mg IV/PO
- Ranitidine 50 mg IV OR Famotidine 20 mg IV

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

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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

Patients should not be retreated until neutrophil ≥ 1.5 x 10^9 /L and platelet counts ≥ 100 x 10^9/L.

Dose levels: 80 mg/m², 70 mg/m², 60 mg/m². Dose re-escalations are not allowed. Discontinue treatment if toxicity recurs after 2 dose reductions.

Toxicity (Grade or Counts x 10^9/L)	**Paclitaxel dose**
ANC < 1.5 and/or Platelets < 100	Delay[1]
ANC ≤ 0.8 and/or Platelets ≤ 50	Delay[1]; ↓ 1 level for next dose
Grade 2 neurotoxicity	↓ 1 level
Other Grade 2-3 non-hematological[2, 3] or grade 3 neurotoxicity	Delay[1]; ↓ 1 level
Grade 4 non-hematological[3]; more than 2 weeks delay or more than 2 dose reductions	Discontinue

[1] Delay for up to 2 weeks. Start day 1 of cycle when non-hematologic toxicities recover to ≤ grade 1, platelets ≥ 100 x 10^9 /L, and ANC ≥ 1.5 x 10^9 /L; reduce dose as per table.

[2] Except alopecia, fatigue and nausea. Appropriate symptom management should be provided for vomiting, diarrhea, constipation; dose modifications may not be necessary.

[3] Except infusion reactions. See **Management of Infusion Reactions** table below for dose modifications pertaining to infusion reactions.

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**
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with	• 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.

	pre-medications ± reduced infusion rate.	
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider 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.

Hepatic Impairment

Patients with hepatic impairment may be at risk of toxicity, especially severe myelosuppression.

Suggested are:

Bilirubin and/or AST/ALT	Dose (mg/m^2)
2-4 x ULN	60
>4 x ULN	40 or omit

Renal Impairment

No adjustment required.

Dosage in the Elderly

No adjustment required, but elderly patients are more at risk for severe toxicity.

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F - Adverse Effects

Refer to PACLitaxel 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 (may be permanent) • Musculoskeletal pain (may be severe) • Neuropathy (may be severe, includes cranial nerves and autonomic)	• Diarrhea • Nausea/vomiting • Myelosuppression +/- infection and bleeding (may be severe) • Hypersensitivity (may be severe)	• Hypotension • ECG changes • Mucositis • Edema • Fatigue • ↑ LFTs (may be severe)	• Arrhythmia • Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Injection site reactions • Rash • GI obstruction • GI perforation • Pancreatitis • Secondary malignancy • Encephalopathy • Seizures • Cystoid macular edema • Pneumonitis • Typhlitis • Radiation recall

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G - Interactions

Refer to PACLitaxel drug monograph(s) for additional details

- Caution with concurrent use of CYP2C8/3A4 substrates, inhibitors and inducers

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H - Drug Administration and Special Precautions

Refer to PACLitaxel drug monograph(s) for additional details

Administration

- 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 Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL and infuse over 3 hours.
- For weekly dosing, may be infused over 1 hour - mix in 250mL bag as above (not approved by manufacturer).
- 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.

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 reactions to paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with severe baseline neutropenia (<1.5 x 10^9/L; < 1 x 10^9/L for patients with AIDS-related Kaposi's)

Warning/Other Precautions:

- 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/Lactation:

- Paclitaxel is 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: Yes

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC at baseline and at each visit
- Baseline and regular liver and renal function tests
- Blood pressure and pulse rate monitoring during infusion, cardiac monitoring with prior arrhythmia
- Clinical assessment of infection, bleeding, musculoskeletal, neurologic (sensory), hypersensitivity, flu-like symptoms and GI toxicity; regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Renal function tests (AIDS-related Kaposi's sarcoma); Baseline and before each dose

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	18.663 minutes
Nursing Workload (average time per visit)	39.833 minutes

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K - References

Paclitaxel drug monograph, Cancer Care Ontario.

Joly F, Houédé N, Noal S, et al. Do patients with advanced urothelial carcinoma benefit from weekly

paclitaxel chemotherapy? A GETUG phase II study. Clin Genitourin Cancer 2009 Aug;7(2):E28-33.

Vaughn DJ, Broome CM, Hussain M, et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002;20(4):937-40.

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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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