Drug Monograph

A - Drug Name

PACLitaxel

COMMON TRADE NAME(S): Taxol®

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B - Mechanism of Action and Pharmacokinetics

Paclitaxel promotes assembly of microtubules and stabilizes them against depolymerization. It also inhibits cell replication by blocking cells in the late G2 and/or M phases of the cell cycle. Paclitaxel is obtained via a semi-synthetic process from *Taxus baccata*.

Distribution	Extensive extravascular distribution and/or tissue binding.	
	Cross blood brain barrier?	no
	PPB	89 %
Metabolism	Hepatic metabolism (CYP 2C8 and CYP 3A4) and biliary secretion. Non-linear pharmacokinetics.	
	Active metabolites	no information found
	Inactive metabolites	Hydroxylated metabolites
Elimination	High concentrations found in bile; 71% excreted in feces in 120 hours (5% unchanged)	
	Urine	1.3 to 12.7 % as unchanged drug.

Half-life	9.9 hours (3 hour infusion)

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C - Indications and Status

Note: There are multiple generic brands, and not all of the indications listed below are contained in each product monograph. However, the indication is listed if approved for at least one generic brand

Health Canada Approvals:

- Breast cancer (adjuvant and second-line metastatic)
- Non-small cell lung cancer (first-line advanced)
- Ovarian cancer (first-line combination, second-line metastatic)

Other Uses:

- Breast cancer (neoadjuvant)
- Gastrointestinal cancer (anal, gastroesophageal)
- Genitourinary cancer (penile, prostate, bladder, testicular)
- Gynecological cancer (cervical, germ cell, gestational trophoblastic disease, vulvar, gynecological sarcoma, endometrial, fallopian tube, primary peritoneal)
- Head and neck cancer
- Thyroid cancer
- Thymoma
- Ewing's sarcoma
- Kaposi's sarcoma
- Skin cancer (Merkel cell, Melanoma)
- Cancer of unknown primary origin

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following data were based on clinical trials in ovarian and breast cancer patients, who were treated with single agent paclitaxel 175 mg/m^2 IV over 3 hours.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (3%) (transient, including bradycardia)	I
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	E D
	ECG changes (14%)	E
	Hypotension (11%)	I
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (93%) (rarely permanent)	E
	Nail disorder (2%)	E D
	Radiation recall reaction (rare)	I
	Rash (rare- may be severe)	I E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Dehydration	E
	Diarrhea (25%) (may be severe - typhlitis)	I E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Mucositis (20%) (may be severe)	E
	Nausea, vomiting (44%)	I
	Typhlitis (rare)	I
General	Edema (21%)	E
	Fatigue (17%)	E
Hematological	Myelosuppression ± infection, bleeding (grade 4 neutropenia 27%)	E
Hepatobiliary	↑ LFTs (18%) (severe- rare)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (40%) (severe 1%)	I

Injection site	Injection site reaction (4%) (may be severe)	I
Musculoskeletal	Musculoskeletal pain (54%) (severe 12%)	E
Neoplastic	Secondary malignancy (rare)	L
Nervous System	Ataxia (rare)	E
	Autonomic neuropathy (rare)	E
	Encephalopathy (rare)	E
	Optic neuritis / Ototoxicity (rare)	E
	Peripheral neuropathy (64%) (severe 4%)	E
	Seizure (rare)	E
	Syncope (rare)	E
Ophthalmic	Cystoid macular edema (rare)	E
	Eye disorders (visual disturbances- rare)	E
	Optic nerve disorder (rare)	E
Respiratory	Pneumonitis (rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse events are alopecia, peripheral neuropathy, musculoskeletal pain, nausea/vomiting, hypersensitivity, myelosuppression, diarrhea, edema, mucositis, ↑ LFTs.

Myelosuppression is dose and schedule-dependent but is not cumulative, with neutropenia being less common when paclitaxel was given as a 3-hour infusion as compared to a 24-hour infusion schedule. Toxicity may be more severe in HIV patients, especially infection (febrile neutropenia and opportunistic infections) and neutropenia.

Congestive heart failure (including LVEF decrease) has been reported in patients who have received other chemotherapy agents, especially anthracyclines.

Hypersensitivity reactions typically occur in early treatment courses and within the first hour of infusion. Dyspnea, flushing, chest pain and tachycardia were the most frequent manifestations. Reactions are neither dose-related nor dependent on prior exposure to paclitaxel, and may be caused by histamine release mediated by the Cremophor EL diluent. Because of the significant risk of hypersensitivity reactions, the patient must be monitored closely; a physician must be readily available, as well as emergency medications and resuscitation equipment. Anaphylaxis and severe hypersensitivity reactions (hypotension, angioedema, generalized urticaria) occur in 2% of patients and may rarely be fatal.

Myalgia and/or arthralgia tend to appear 2-3 days after paclitaxel administration and resolve within a few days, and do not appear to be dose-related. Non-steroidal anti-inflammatory drugs are successful in relieving these symptoms.

Peripheral neuropathy may be dose-limiting and is dose-related and cumulative. Common symptoms include numbness, tingling and/or burning pain in a glove-and-stocking distribution. Mild symptoms usually improve or resolve completely within several months after discontinuation of therapy. Pre-existing neuropathies are not a contraindication to treatment with paclitaxel.

Central neurotoxicity may occur and may be severe, especially in children treated at high dosage.

Hypotension and **bradycardia** have been observed during paclitaxel infusion and are usually asymptomatic, but not dose or schedule-dependent. Severe cardiovascular events, including death, have been reported; if these occur, appropriate action should be taken and the dose interrupted/discontinued; continuous electrocardiographic monitoring should be performed if patient receives subsequent paclitaxel therapy.

Cystoid macular edema (CME) has been reported in paclitaxel-treated patients, as well as with other taxanes. Patients who present with impaired vision during treatment should undergo a prompt ophthalmologic examination. Taxane-associated CME may not be associated with vascular leakage and is usually reversible upon taxane discontinuation. Treatment for CME may be required in some cases.

Pseudomembranous colitis has been reported in patients who were not taking concomitant antibiotics.

Paclitaxel has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of paclitaxel. Recurrent injury to a previously radiated site may occur weeks to months following radiation. Recall skin reactions at a site of previous extravasation, after paclitaxel administration at a different site, have been reported rarely.

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E - Dosing

Refer also to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medications* (prophylaxis for infusion reaction):

Pre-Medications for Q3W 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

Pre-Medications for weekly paclitaxel: (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.

† 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.

Adults:

Start treatment only in patients with neutrophils ≥ 1.5 x 10^9/L (≥ 1 x 10^9/L in AIDS-related Kaposi's sarcoma) and platelet counts ≥ 100 x 10^9/L

Intravenous: 175 mg/m² over 3 hours every 3 weeks

Refer to the regimen monographs for disease site-specific or combination regimen dosing.

Dosage with Toxicity:

Worst toxicity in previous cycle	Dose of paclitaxel
Febrile neutropenia Grade 4 ANC ≥ 5-7 days Grade 4 thrombocytopenia	↓ by 20%*
Grade 3 neurotoxicity, mucositis, or other toxicity	↓ by 20%*
Grade 4 neurotoxicity or other toxicity, any grade cystoid macular edema	Discontinue
*Patients should not be retreated with paclitaxel until neutrophils ≥ 1.5 x 10^9/L (≥ 1.0 x 10^9/L in AIDS-related Kaposi's sarcoma) and platelet counts ≥ 100 x 10^9/L and other toxicity has 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
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• 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. • 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.

Dosage with Hepatic Impairment:

Caution and dose reduction advised in patients with moderate to severe hepatic impairment.

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

Suggested are:

Bilirubin		**AST/ALT**	**Dose (% usual dose)**
≤1.25 x ULN	And	2-10 x ULN	75%
1.26 to 2.5 x ULN	And	<10x ULN	40%
2.6 to 4 x ULN	And	<10x ULN	25%
>4 x ULN	And/Or	≥10 x ULN	Consider risk-benefit or Omit

Dosage with Renal Impairment:

No adjustment required, but may consider for patients with HIV-AIDS if creatinine ≥ 2 x ULN

Dosage in the elderly:

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

Children:

Safety and efficacy have not been established. Children may be at a higher risk of severe and sometimes fatal neurologic toxicity, especially with high doses, possibly related to the ethanol content of paclitaxel infusions.

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F - Administration Guidelines

- 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 an in-line filter no greater than 0.22 microns).
- 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.
- 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.
- Paclitaxel should be given before cisplatin, if given in combination (refer to drug interactions section)
- 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.

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G - Special Precautions

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 sarcoma)

Other Warnings/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.

Other Drug Properties:

- Carcinogenicity:
  Acute myeloid leukemia and myelodysplastic syndrome have been reported post-marketing.

Pregnancy and Lactation:

- Genotoxicity: Yes
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
  Paclitaxel is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** (general recommendation) after the last dose.
- Excretion into breast milk: Probable
  Breastfeeding is not recommended.
- Fertility effects: Probable
  Documented in animal studies

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H - Interactions

The drugs listed in this table are based on drug interaction case reports, pharmacokinetic studies, or potential interactions. Paclitaxel clearance was not affected by cimetidine administration pre-treatment.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cisplatin	↑ myelosuppression, neurotoxicity, or ↑ risk of renal failure observed when paclitaxel given after cisplatin	↓ paclitaxel clearance by 33% when paclitaxel given after cisplatin	Give paclitaxel before cisplatin; monitor for toxicity
Doxorubicin (after prolonged paclitaxel infusions)	↑ neutropenia and stomatitis	Higher plasma levels of doxorubicin and doxorubicinol	Caution
Epirubicin	↑ systemic exposure to epirubicin or its metabolites. May be schedule-dependent.	Taxane or cremophor EL possibly compete with epirubicin for biliary excretion	Caution if used in combination; give epirubicin first
Cyclophosphamide (given after paclitaxel)	↑ myelosuppression	Unknown	Caution
Radiation	Radiation pneumonitis	↑ pulmonary effects	Avoid/caution
Carboplatin (given after paclitaxel)	↓ thrombocytopenia	Unknown	Caution

CYP 2C8 substrates (i.e. paclitaxel, sorafenib, amiodarone)	May ↑/↓ effects of substrates or paclitaxel	Altered metabolism of CYP2C8 substrates or paclitaxel	Caution
CYP 3A4 substrates (i.e., verapamil, etoposide, dexamethasone, vincristine)	May ↑/↓ effects of substrates or paclitaxel	Altered metabolism of CYP3A4 substrates or paclitaxel	Caution
Inducers of CYP 2C8 (i.e., phenobarbital)	May ↓ paclitaxel levels and effects	↑ metabolism of paclitaxel	Caution
CYP 2C8 inhibitors (i.e. gemfibrozil, montelukast)	May ↑ paclitaxel levels and effects	↓ metabolism of paclitaxel	Caution
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	May ↓ paclitaxel levels and effects	↑ metabolism of paclitaxel	Caution
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	May ↑ paclitaxel levels and effects	↓ metabolism of paclitaxel	Caution

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each visit
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and as clinically indicated
Blood pressure and pulse	During infusion (more frequently during the first hour), or per usual institutional protocol
Continuous cardiac monitoring in patients who developed serious conduction abnormalities	During subsequent infusions
Ophthalmology if visual impairment	As clinically indicated
Clinical assessment of bleeding, infection, diarrhea, mucositis, musculoskeletal, neurologic (sensory), hypersensitivity, injection site reaction, respiratory, thromboembolism	At each visit

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

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K - References

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November 2024 Modified Adverse effects, Dose modifications, Interactions and Monitoring sections

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L - Disclaimer

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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