DRUG NAME: Paclitaxel

SYNONYM(S): benzenepropanoic acid[1]

COMMON TRADE NAME(S): TAXOL®, ONXOL®

CLASSIFICATION: antimicrotubule agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Paclitaxel is a taxane. Paclitaxel binds to tubulin, the protein component of microtubules, simultaneously promoting their assembly and disassembly to form stable, nonfunctional microtubules.[1,2] Although some reports indicate a cross-reactivity rate of 90% between docetaxel and paclitaxel, others suggest it does not occur consistently.[2,3] Stabilization of microtubules blocks cells in the M phase of the cell cycle, inhibiting cell division and causing cell death.[2] Paclitaxel acts as a radiosensitizing agent by blocking cells in the G_2phase.[4] Paclitaxel is an immunosuppressant.[5,6]

PHARMACOKINETICS:

Oral Absorption	no information found	
Distribution	biphasic: initial distribution to peripheral compartment, then slow efflux from the peripheral compartment; widely distributed into body fluids and tissues[1,7]; small changes in dose may lead to large changes in peak plasma concentrations and total drug exposure due to saturable, nonlinear pharmacokinetics[2]	
	cross blood brain barrier?[2,8]	no
	volume of distribution[1,2,5,6]	67 L/m² for 1-6 h infusion; varies with dose and infusion time; 198-688 L/m² for 24 h infusion
	plasma protein binding[1,2,5]	88-98%
Metabolism	extensively metabolized in liver via CYP 2C8 (primarily) and CYP 3A4; activity of metabolites is unknown[1,2,7]	
	metabolite(s)[2,4,9]	• 67% as 6α-hydroxypaclitaxel via CYP 2C8; • 37% as 3-p-hydroxypaclitaxel and 6α,3-p-dihydroxypaclitaxel via CYP 3A4
Excretion	primarily via bile[1,2,5,7,8]	
	urine	14% (1-13% as unchanged drug)
	feces	71% (5% as unchanged drug)
	terminal half life[1,2,6,7]	10 h; varies with dose and infusion time
	clearance[1,2,7]	12 L/h/m²; varies with dose and infusion time
Children[2]	clearance: 19 to 260 L/m²	

Adapted from standard reference[7] unless specified otherwise.

USES:

Primary uses:
*Breast cancer
*Lung cancer, non-small cell
*Ovarian cancer
*Kaposi's Sarcoma

Other uses:
Lung cancer, small cell[2]
Esophageal cancer[2]
Bladder cancer[2]
Head and Neck cancer[2]
Cervical cancer[2]
Endometrial cancer[2]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- ***Preexisting liver impairment*** may impair elimination of paclitaxel[1,7]; dose reduction is suggested[2,9]; see **Dosage Guidelines**.

Special populations:
- ***Elderly patients*** may have more myelosuppression, neuropathy and cardiovascular toxicities[2]
- Patients with ***AIDS-related Kaposi's sarcoma*** may have more hematologic toxicities, infections and febrile neutropenia.[7]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Paclitaxel is clastogenic in human lymphocytes *in vitro* but not in other mammalian *in vivo* chromosome tests.[1,2,7]

Fertility: In animal studies, reduced fertility has been observed, with decreased pregnancy rates and increased embryo loss in females and testicular atrophy/degeneration in males.[1,2]

Pregnancy: FDA Pregnancy Category D.[5,10] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Paclitaxel has shown to be embryotoxic and fetotoxic in animal studies; soft tissue and skeletal malformations have been reported.[1,2,7]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1,2,7]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials.[11-14]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (62-78%, severe 6-16%)[1,7]
	febrile neutropenia (2%)[6]
	leukopenia (86-90%, severe 4-17%)[1,7]
	neutropenia (87-90%, severe 27-52%)[1,2,7]; nadir 10-12 days, recovery 15-21 days; may require dose reduction
	thrombocytopenia (6-20%, severe 1-7%)[1,2,7]; nadir 8-9 days[2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	bradycardia (3-4%); first 3 h of infusion[1,7]; see paragraph following **Side Effects** table
	cardiovascular events (severe 1-2%)[1,7]; see paragraph following **Side Effects** table
ear and labyrinth	hearing loss, tinnitus, vertigo, ototoxicity (<1%)
eye	optic nerve and/or visual disturbances, photopsia, visual floaters (<1%); generally reversible, may be dose-related
gastrointestinal	*emetogenic potential: low-moderate*[15]
	abdominal pain; with intraperitoneal administration[6]
	anorexia (25%)[1]
	constipation (18%)[1]
	diarrhea (25-79%)
	intestinal obstruction (4%)[1]
	mucositis (20-31%); more common with 24 h infusion[1,7]
	nausea and vomiting (44-52%)
	taste changes[2]
general disorders and administration site conditions	*extravasation hazard: irritant*,[16,17] *treat as vesicant*[18]; see paragraph following **Side Effects** table
	edema (17-21%, severe 1%); localized under skin at no specific site
	fever (12%)[7]
	injection site reactions (4-13%)[1,7]
immune system	***hypersensitivity reactions*** (5-42%, severe 1-2%)[1,7,19]; see paragraph following **Side Effects** table
infections and infestations	infections (18-30%, severe 1%); primarily urinary tract and upper respiratory tract[1,7]
injury, poisoning, and procedural complications	radiation recall dermatitis[2]
investigations	***ECG abnormalities*** (8-14%, severe <1%)[1,2,7]; see paragraph following **Side Effects** table
	alkaline phosphatase, elevated (18-22%, severe 1%)[1,7]
	AST, elevated (18-19%, severe 1%)[1,7]
	bilirubin, elevated (4-7%, severe 1%)[1,7]
musculoskeletal and connective tissue	***arthralgia/myalgia*** (54-60%, severe 8-12%)[1,7]; see paragraph following **Side Effects** table
nervous system	autonomic neuropathy, resulting in paralytic ileus and orthostatic hypotension (<1%)
	motor neuropathy, with resultant minor distal weakness (<1%)
	peripheral neuropathy (52-64% severe 2-4%)[1,7]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	dyspnea (2%)[5,6]
	radiation recall pneumonitis[2]
skin and subcutaneous tissue	***alopecia*** (87-93%)[1,7]; usually complete, generally occurs 14-21 days after administration of paclitaxel; onset sudden, often occurring in a single day[2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	nail discolouration (2%)[7]
	rash (12-14%)[1,7]
vascular	hypotension (11-24%); during first 3 h of infusion[1,7]
	phlebitis[1,7]

Adapted from standard reference[7] unless specified otherwise.

Arthralgia/myalgia may be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of paclitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after paclitaxel administration, and resolving within days.[2,7] If arthralgia/myalgia is not relieved by adequate doses of ibuprofen, or short-term, low-dose dexamethasone or prednisone[20,21], gabapentin may be tried.[20-22] Dose reducing paclitaxel may lessen the severity of arthralgias/myalgias; however, there is no data on efficacy of reduced doses in a curative setting. Dose reduction should be considered only if symptom severity precludes continuing paclitaxel.[11,12,23]

Cardiovascular effects present as bradycardia, hypotension and ECG changes. Bradycardia and hypotension typically occur during the first 3 hours of infusion; however, they are usually asymptomatic and do not require treatment. Paclitaxel administration may require interruption or discontinuation in some cases. Frequency of hypotension and bradycardia is not influenced by dose, schedule or prior anthracycline therapy. Common ECG changes are non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia, and premature beats. Among patients with normal ECG at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities. Severe cardiovascular effects are rarely reported, including cases of atrial fibrillation, supraventricular tachycardia, myocardial infarction, congestive heart failure, and thromboembolic events. When reported, these patients had underlying disease or previous radiotherapy or chemotherapy which was thought to have contributed to the event.[2,7]

Paclitaxel ***extravasation*** may rarely cause local tissue necrosis, leading to the suggestion that paclitaxel may have vesicant properties. In some reports, patients have experienced recall reactions from previous paclitaxel extravasations. No correlation has been made between concentration or volume of paclitaxel extravasated and the risk of tissue necrosis. Extravasation injuries due to paclitaxel may be either immediate or delayed and thus patients may require an extended follow-up; patient complaints of pain, burning, or stinging at the injection site occurring several days after the infusion should be investigated. Specific treatment recommendations for paclitaxel extravasation are still unclear as experience is anecdotal.[7,16,17] For management of extravasation reactions, see BCCA Policy Number III-20 ***Prevention and Management of Extravasation of Chemotherapy.***

Hypersensitivity reactions typically occur within the first 10 minutes of the first two cycles.[2,24] Reactions are caused by either a histamine release in response to polyoxyl 35 castor oil (Cremophor® EL), or a non-IgE mediated reaction to the taxane moiety. Frequent, minor hypersensitivity reactions include: flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). Chills, abdominal pain, and back pain are more rare.[2,7] Severe hypersensitivity reactions include: dyspnea requiring bronchodilators, hypotension requiring treatment, flushing, chest pain, tachycardia, angioedema, and generalized urticaria. Severe reactions rarely occur after the third cycle of treatment.[2,7] The incidence and severity of hypersensitivity reactions are reduced with premedication although rare, fatal reactions may occur despite premedication.[7]. A single IV dexamethasone dose with an antihistamine and an H_2-antagonist reduces the incidence of hypersensitivity reactions from 40% to 2-3%.[7,25] The frequency and severity of hypersensitivity reactions are not affected by the dose or duration of infusion of paclitaxel.[7,26] For management of hypersensitivity reactions, see ***BCCA Protocol Summary for Management of Hypersensitivity Reactions to Chemotherapeutic Agents***.

Rechallenge after a severe hypersensitivity reaction:
The occurrence of hypersensitivity reactions does not preclude rechallenge with paclitaxel. In the event of a hypersensitivity reaction, the patient may be rechallenged the same day after additional premedication, slowing the rate of infusion, and close monitoring.[23,25] Subsequent cycles may benefit from a regimen of oral dexamethasone

given 12 and 6 hours before paclitaxel, plus antihistamines and H_2-antagonists given 30 minutes to 1 hour before paclitaxel.[24,26,27] Consider substituting paclitaxel with docetaxel or implementing a desensitization protocol if a patient develops a reaction following a rechallenge.[24] For management of hypersensitivity reactions, see ***BCCA Protocol Summary for Management of Hypersensitivity Reactions to Chemotherapeutic Agents*** or refer to protocol by which patient is being treated.

Peripheral sensory neuropathy presents with numbness and tingling in a stocking-and-glove distribution, perioral numbness, and hyperesthesia. Onset of symptoms can be within days following infusion. Frequency of symptoms increases with repeated exposure and cumulative dose.[2,7] Pre-existing neuropathies from prior therapies are not a contraindication for treatment with paclitaxel; however, the incidence of neuropathy appears to be increased in this patient population. A dose reduction of 20% is recommended for all subsequent cycles of paclitaxel for patients who experience severe peripheral neuropathy. Sensory neuropathy usually improves or resolves within months of paclitaxel discontinuation.[7]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin[2,7,28]	may increase neutropenia when paclitaxel is given *after* cisplatin	paclitaxel clearance is decreased by 25-33% when given *after* cisplatin	preferred method is to give paclitaxel first when administering as sequential infusions
dexamethasone[1,7]	does not affect protein binding of paclitaxel		
diphenhydramine[1]	does not affect protein binding of paclitaxel		
disulfiram[29]	development of acute alcohol intolerance reactions	inhibition of aldehyde dehydrogenase by disulfiram, leading to development of toxic metabolites of ethanol (found in the solution)	avoid disulfiram concurrently with paclitaxel administration
doxorubicin[2,7,28]	may increase cardiac toxicity from doxorubicin when given concurrently with paclitaxel	doxorubicin clearance is decreased leading to increased plasma levels of doxorubicin and doxorubicinol	monitor for increased cardiotoxicity
metronidazole and derivatives[29]	development of acute alcohol intolerance reactions; the risk for most patients appears slight	inhibition of aldehyde dehydrogenase by metronidazole, leading to development of toxic metabolites of ethanol (found in solution)	avoid metronidazole and its derivatives concurrently with paclitaxel administration
vaccines, live[29]	enhanced viral replication may increase the risk of disseminated disease	decreased immune response allows live vaccine to produce infection	avoid live vaccines during treatment
warfarin[29]	may increase anticoagulant effect of warfarin when given concurrently with paclitaxel	paclitaxel may displace warfarin from plasma protein binding sites when given concurrently	monitor INR and adjust warfarin dosing accordingly; consider use of LMWH with chemotherapy[30]

Paclitaxel is a **substrate** of CYP 3A4 and CYP 2C8 isoenzymes. Strong inhibitors of CYP 3A4 or 2C8 may decrease paclitaxel metabolism resulting in increased plasma levels and toxicity. Avoid concurrent use if possible; if unavoidable, consider reducing the

paclitaxel dose.[2,7,28] Strong inducers of CYP 3A4 or 2C8 may increase paclitaxel metabolism, potentially resulting in a reduced therapeutic effect of paclitaxel.[1,2,7]

SUPPLY AND STORAGE:

***Injection*:**
Accord Healthcare Inc. supplies paclitaxel as 30 mg, 100 mg, and 300 mg vials in a concentration of 6 mg/mL. Store at room temperature. Product may precipitate if refrigerated; precipitate redissolves at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 39.1%(w/v) ethanol.[31]

Biolyse Pharma supplies paclitaxel as 30 mg and 100 mg single dose vials and a 300 mg multi-dose vial in a concentration of 6 mg/mL. Refrigerate. Do not freeze. Potency is not affected when transported or stored for up to 2 months at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 49.7%(v/v) alcohol.[1]

Bristol-Myers Squibb Canada supplies paclitaxel as 30 mg, 100 mg, and 300 mg vials in a concentration of 6 mg/mL. Store at room temperature. Product may precipitate if refrigerated; precipitate redissolves at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 49.7%(v/v) ethanol.[7]

Hospira Healthcare supplies paclitaxel as 30 mg, 100 mg, 150 mg, and 300 mg multi-use vials in a concentration of 6 mg/mL. Store at room temperature. Protect from light. If refrigerated, product may precipitate; precipitate redissolves at room temperature. Non-medicinal ingredients per mL of solution: 527 mg Cremophor® EL (polyethoxylated castor oil) and 46.5%(v/v) alcohol.[32]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- Concentrated solution must be diluted prior to IV infusion.[1,7]
- To prevent extraction of plasticizer DEHP from container, prepare solutions in non-DEHP containers and administer using non-DEHP administration sets.[1,7]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not recommended; dilution required prior to administration[1,7]
Intermittent infusion	***over 1-3 h*** (use non-DEHP administration sets)[5,33-35]
Continuous infusion	has been given[1,7]
Intraperitoneal	***infuse into abdominal cavity as rapidly as possible by gravity*** (use non-DEHP equipment)[2,36,37]

BCCA administration guideline noted in ***bold***, ***italics***

	hyperthermic intraperitoneal chemotherapy (HIPEC): pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[38,39]
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks***[40,41]:	***80 mg/m^2 IV for one dose on days 1, 8 and 15*** (total dose per cycle 240 mg/m^2)
	3 weeks[42-58]:	***175 mg/m^2*** (range 135-175 mg/m^2) ***IV for one dose on day 1*** (total dose per cycle 135-175 mg/m^2)
	3 weeks[59-62]***:***	***200 mg/m^2 IV for one dose on day 1*** (total dose per cycle 200 mg/m^2)
	4 weeks[33,34,40,63-65]	***80 mg/m^2 IV for one dose on days 1, 8, 15 and 21*** (total dose per cycle 320 mg/m^2)
	4 weeks[66]:	***110 mg/m^2 IV for one dose on days 1, 8 and 15*** (total dose per cycle 330 mg/m^2)
Premedication regimen[2,7,19,25,26,63,67]*:*	***30 minutes before paclitaxel: dexamethasone 20 mg IV plus diphenhydramine 50 mg IV plus ranitidine 50 mg IV***	
	alternate regimen: 12 h and 6 h before paclitaxel: dexamethasone 20 mg PO plus 30 minutes before paclitaxel: diphenhydramine 50 mg IV plus ranitidine 50 mg IV	
Concurrent radiation:	has been given[7]	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
Dosage in renal failure[1,6]*:*	no dosage adjustment required for creatinine clearance less than 50 mL/min	

BCCA usual dose noted in ***bold, italics***

Dosage in hepatic failure[2,6]*:*

Cycle Length:
Suggested guidelines for first course; subsequent courses should be based on individual tolerance

ALT or AST		bilirubin	dose
<10 X ULN	and	≤1.25 X ULN	175 mg/m²
<10 X ULN	and	1.26-2 X ULN	135 mg/m²
<10 X ULN	and	2.01-5 X ULN	90 mg/m²
≥10 X ULN	or	>5 X ULN	not recommended

Dosage in dialysis:

hemodialysis: no significant removal[2]; may give standard dose before or after hemodialysis[68-70]

chronic ambulatory peritoneal dialysis(CAPD): no significant removal; may give standard dose before or after CAPD[69-71]

Children:

Intravenous:

Cycle Length:
3 weeks[8,72]: 135-250 mg/m² IV for one dose on day 1
3 weeks[73,74]: 200-350 mg/m² IV for one dose on day 1

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