

**DRUG NAME: Paclitaxel****SYNONYM(S):** NSC-125973<sup>1</sup>**COMMON TRADE NAMES:** generic available, ONXOL® (USA), TAXOL®**CLASSIFICATION:** antimicrotubule agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:** Paclitaxel is an antimicrotubule agent that promotes the assembly and stabilization of microtubules from tubulin dimers.<sup>2</sup> Late G2 mitotic phase is inhibited and thus cell replication is inhibited.<sup>3</sup> Paclitaxel also can distort mitotic spindles resulting in chromosomal damage.<sup>3</sup>**PHARMACOKINETICS:**

Interpatient variability	no information found	
Oral Absorption	not absorbed orally	
Distribution	biphasic; initial rapid distribution to the peripheral compartment, then a slow efflux of paclitaxel from the peripheral compartment; widely distributed into body fluids and tissues; affected by dose and duration of infusion <sup>3</sup>	
	cross blood brain barrier?	no
	volume of distribution	198-688 L/m <sup>2</sup> ; varies with dose and infusion time
	plasma protein binding	89-98% <sup>3</sup>
Metabolism	hepatic via the cytochrome P450 isozymes CYP2C8/9 and CYP3A4	
	active metabolite(s)	primarily 6 $\alpha$ -hydroxypaclitaxel
	inactive metabolite(s)	yes
Excretion	elimination follows non-linear (saturable) pharmacokinetics <sup>4,5</sup> ; high concentrations found in bile	
	urine	14% (1.3-12.6% as unchanged drug) <sup>3</sup>
	feces	71% (5% as unchanged drug)
	terminal half life	3.0-52.7 h; varies with dose and infusion time (e.g., 3 h infusion of 175 mg/m <sup>2</sup> : 9.9 h)
	clearance	11.6-24.0 L/h/m <sup>2</sup> ; varies with dose and infusion time (e.g., 3 h infusion of 175 mg/m <sup>2</sup> : 12.4 L/h/m <sup>2</sup> )
Gender	no information found	
Elderly	clearance <sup>6</sup>	11.4-16.2 L/h/m <sup>2</sup>
Children	terminal half life <sup>3</sup>	4.6-17 h
Ethnicity	no information found	

Adapted from standard reference<sup>7</sup> unless specified otherwise.

**USES:****Primary uses:**

- \* Breast cancer
- Cervical cancer<sup>8</sup>
- Endometrial cancer<sup>9</sup>
- \* Kaposi's Sarcoma
- \* Lung cancer
- \* Ovarian cancer

**Other uses:**

- Bladder cancer<sup>3</sup>
- Head and neck cancer<sup>3</sup>
- Leukemias<sup>3</sup>
- Malignant melanoma<sup>3</sup>

\*Health Canada approved indication

**SPECIAL PRECAUTIONS:**

**Hypersensitivity reactions (HSR)**<sup>7</sup>: Paclitaxel infusions may be associated with acute hypersensitivity reactions; incidence is significantly reduced by premedication and increased infusion times. For more information refer to the hypersensitivity reaction paragraph following the side effect table.

**Carcinogenicity**: Not yet studied.<sup>10</sup>

**Elderly patients** are at an increased risk for developing toxicities (e.g., arthralgia, myalgia, neutropenia, neuropathy).<sup>3</sup>

**Mutagenicity**<sup>7</sup>: Paclitaxel was not mutagenic in the Ames test. Paclitaxel was clastogenic in the mammalian *in vitro* and *in vivo* chromosome tests.

**Fertility**: The effects of paclitaxel on fertility have not been established. Women of childbearing potential should be counselled to avoid pregnancy.<sup>8</sup>

**Pregnancy**: FDA Pregnancy Category D. 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).

**Breastfeeding** is not recommended due to the potential secretion into breast milk.<sup>10</sup>

**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, and/or determined to be clinically important.<sup>9,11</sup> When placebo-controlled trials are available, adverse events are included if the incidence is  $\geq$  5% higher in the treatment group, and the frequencies provided are compared to the incidence in the placebo-controlled arms of the trials.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
allergy/immunology	<b><i>hypersensitivity reactions (severe 1%)</i></b>
blood/bone marrow/ febrile neutropenia	anemia (62%, severe 6%)
	<b><i>neutropenia (severe 6-21%)<sup>3</sup>; nadir 8-11 days, recovery 15-21 days</i></b>
	thrombocytopenia (6%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
cardiovascular (arrhythmia)	arrhythmias <sup>8</sup> (1%) (e.g., asymptomatic ventricular tachycardia, atrial fibrillation, supraventricular tachycardia, junctional tachycardia) bradycardia (25%); during infusion, transient <sup>3</sup>
cardiovascular (general)	electrocardiogram abnormalities (23%)
	edema (21%)
	hypertension (1%)
	hypotension (24%); during infusion, transient
	myocardial infarction (rare)
constitutional symptoms	fever (12%); febrile neutropenia
dermatology/skin	<i>extravasation hazard<sup>12</sup>: irritant</i>
	<b><i>alopecia (87%)<sup>3,13</sup>; usually complete, generally occurs 14-21 days after administration of paclitaxel with a sudden onset, often occurring in a single day<sup>8</sup></i></b>
	flushing (28%) <sup>3</sup>
	<b><i>nail and skin changes (2%)<sup>11</sup>; mild, transient</i></b>
	<b><i>radiation recall reaction (rare)<sup>13</sup></i></b>
	rash (12%) <sup>3</sup>
gastrointestinal	<i>emetogenic potential<sup>14</sup>: low</i>
	anorexia (25%)
	constipation (18%)
	diarrhea (38%)
	<b><i>intestinal obstruction (4%)<sup>11</sup></i></b>
	mucositis (31%); more common with 24 h infusion
	<b><i>nausea (52%)<sup>13</sup>; mild to moderate</i></b>
	stomatitis (15%) <sup>3</sup> ; most common at doses >390 mg/m <sup>2</sup>
	taste perversion <sup>8</sup>
	vomiting (5-6%); mild to moderate <sup>3</sup>
hepatic	hepatic necrosis and hepatic encephalopathy (rare)
infection	febrile neutropenia (12%)
neurology	ataxia (<1%) <sup>3</sup>
	encephalopathy (rare)
	ethanol intoxication <sup>3</sup>
	seizures (rare)
	myopathy (25-50%) <sup>3</sup>
	<b><i>peripheral neuropathy (64%, severe 4%)</i></b>
metabolic/laboratory	mild increase in liver enzymes (18%)
ocular/visual	optic nerve and/or visual disturbances (rare)
pain	<b><i>arthralgia/myalgia (54%, severe 12%)</i></b>

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b><i>bold, italics</i></b>	
pulmonary	interstitial pneumonia, lung fibrosis (rare)
vascular	pulmonary embolism (rare)
	phlebitis (2%) <sup>3</sup>

Adapted from standard reference<sup>7</sup> unless specified otherwise.

**Hypersensitivity reactions (HSR)** are common with paclitaxel and appear to be due to a nonimmunologically-mediated release of histamine and other vasoactive substances.<sup>3</sup> The exact cause is not known but may result from either the Cremophor EL in the paclitaxel injection or from the paclitaxel itself.<sup>8</sup> HSR most often occur in the first hour of an infusion (75% occur within the first 10 minutes).<sup>3</sup> The frequency and severity of these reactions are not affected by the dose or schedule of paclitaxel administration.<sup>15</sup> Delayed onset of urticarial rash, 7-10 days following completion of a course of treatment, has been seen in some Kaposi's sarcoma patients.<sup>8</sup>

Incidence of HSR are significantly reduced by premedication. Corticosteroids (e.g., dexamethasone), histamine H<sub>1</sub>-antagonists (e.g., diphenhydramine) and H<sub>2</sub>-antagonists (e.g., ranitidine) should be administered prior to paclitaxel administration to minimize the potential for anaphylaxis. The following is one suggested regimen for adults<sup>16-34</sup>:

- 45 minutes before paclitaxel, dexamethasone 20 mg IV
- 30 minutes before paclitaxel, diphenhydramine 50 mg IV and ranitidine 50 mg IV.

A more protracted premedication scheme, which may be more effective, particularly where a patient has exhibited HSR would be: 12 hours and 6 hours before paclitaxel, dexamethasone 20 mg po and then following the above premedication regime.<sup>9</sup> In the event of a treatment delay (e.g., admixture is unavailable), additional doses are required. In premedicated patients, symptoms of HSR are reported in as many as 41%, although severe HSR occur in less than 2% of patients.<sup>15</sup>

The occurrence of HSR does not preclude rechallenge with paclitaxel.<sup>35</sup> If there is a hypersensitivity reaction, the patient may be rechallenged after further premedication and with close monitoring.<sup>35</sup> Prolonging the infusion to  $\geq 6$  hours may decrease the incidence of hypersensitivity reactions<sup>3</sup>; 24, 96 and 120 hour infusions have been studied and show decreased HSR with increased infusion times.<sup>35</sup>

Treatment for hypersensitivity reactions, including general management, and management of hypotension, dyspnea and bronchospasm can be found in the BC Cancer Agency Protocol Summary of Hypersensitivity Reactions to Chemotherapeutic Agents ([SCDRUGRX](#)).<sup>36</sup> See below for general management.

General Management<sup>36</sup>: It is recommended that patients are assessed by a physician if having a reaction requiring the administration of medications or as patient condition warrants.

<p><b>Moderate</b></p> <p>e.g., moderate rash, flushing, pruritus, mild dyspnea, chest discomfort, abdominal discomfort, lower back pain, mild hypotension</p>	<ul style="list-style-type: none"> <li>• Stop infusion.</li> <li>• Give diphenhydramine 25-50 mg IV and/or hydrocortisone sodium succinate 100 mg per physician orders.</li> <li>• After recovery of symptoms, resume infusion at a rate per protocol. If no direction in protocol consider resuming at 25% of previous rate for at least 5 minutes, 50% for at least 5 minutes, 75% for at least 5 minutes and then full rate if no reaction.</li> <li>• Depending on severity of reaction, may increase to full rate at physician's discretion.</li> <li>• Premedication for all future cycles (see Prophylaxis section in SCDRUGRX). Initiate infusion at slower rate (consider 50% of full rate) per physician orders.</li> </ul>
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<p><b>Severe (potentially life threatening)</b></p> <p>i.e., to be used if reaction escalates (e.g., one or more of respiratory distress requiring treatment, angioedema, hypotension requiring therapy)</p>	<ul style="list-style-type: none"> <li>• Stop infusion and do not restart.</li> <li>• Give diphenhydramine 50 mg IV push and/or hydrocortisone sodium succinate 100 mg IV push per physician orders.</li> <li>• Oxygen if needed for dyspnea (see SCDRUGRX).</li> <li>• Normal saline if needed for hypotension (see SCDRUGRX).</li> <li>• Epinephrine or bronchodilators if indicated (see SCDRUGRX).</li> <li>• Either permanently discontinue the drug or attempt to retreat on another occasion after premedication (see SCDRUGRX) and using slower infusion rate.</li> <li>• <i>Initiate Emergency Response System appropriate for facility if patient condition warrant.</i></li> </ul>
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*IF* there is a true anaphylactic reaction with paclitaxel despite premedication and a slow initial infusion rate the patient should not have a further rechallenge.<sup>9,35</sup>

Very rarely, fatal reactions have occurred in patients despite pre-treatment.<sup>10</sup> Docetaxel has been successfully substituted in some patients who experienced severe HSR with paclitaxel,<sup>37-39</sup> however, cross-sensitivity has also been reported.<sup>40</sup>

**Arthralgia/myalgia** is dose and schedule dependent; worse with higher doses and shorter infusions.<sup>41</sup> The symptoms are usually transient, occur within two or three days after paclitaxel administration, and resolve after a few days.<sup>7</sup> If arthralgia/myalgia from paclitaxel is grade 2 (moderate) or higher and is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3®), a suggested symptomatic treatment includes<sup>16-23,25</sup>:

- gabapentin 300 mg po on day prior to paclitaxel, 300 mg po bid on treatment day and then 300 mg po tid x 7-10 days
- prednisone 10 mg po bid x 5 days starting 24 hours post-paclitaxel

In non-curative protocols, if arthralgia/myalgia persists, subsequent paclitaxel dose reduction may be considered.<sup>20-23,26-29,34</sup> In curative settings, there is no data on the efficacy of a reduced dose, so it is not advised unless toxicity is severe and precludes continuing paclitaxel without a dose reduction.<sup>35</sup>

**Peripheral neuropathy** is usually sensory in nature. Paclitaxel-induced neurotoxicity often appears as mild paresthesia characterized by numbness and tingling in a stocking-and-glove distribution.<sup>8</sup> Perioral numbness may also occur, and many patients experience burning pain particularly in the feet.<sup>8</sup> Onset may be rapid, occurring within a few days of an infusion.<sup>8</sup> Frequency and severity are related to cumulative doses; toxicity may be dose-limiting.<sup>8</sup> Sensory manifestations usually improve or resolve several months after discontinuing paclitaxel.<sup>8</sup> Pre-existing neuropathies resulting from prior therapies are not a contraindication for treatment with paclitaxel; however, the incidence of paclitaxel-related neuropathy appears to be increased in this population of patients.<sup>15</sup>

**Bradycardia and hypotension** during paclitaxel administration is usually asymptomatic and generally does not require treatment.<sup>15</sup> In some cases, paclitaxel administration may have to be interrupted or discontinued.<sup>15</sup> Although the manufacturer recommends frequent monitoring of vital signs, particularly during the first hour of administration,<sup>15</sup> this is not the standard of practice at the BC Cancer Agency.<sup>42</sup> Based on nursing experience with paclitaxel administration, and consultation with medical oncology and pharmacy, the BC Cancer Agency has found that clinical observation of patients by nurses for early signs of a reaction is more valuable than taking vital signs every 15 minutes.<sup>42</sup> For more information refer to the hypersensitivity reaction paragraph above. Severe cardiac conduction abnormalities have rarely occurred during paclitaxel therapy.<sup>10</sup> If patients develop significant conduction abnormalities during administration, appropriate treatment should be administered and continuous electrocardiographic monitoring should be performed during subsequent infusions.<sup>10</sup>

**Ethanol** is contained in the paclitaxel formulation at a concentration of 396 mg/mL. Consideration should be given to possible CNS effects including impaired ability to drive and operate machinery.<sup>7,15</sup> CNS toxicity has been reported in pediatric patients receiving high doses of paclitaxel (350-420 mg/m<sup>2</sup> as a 3 hour infusion). This toxicity may have resulted from the ethanol contained in the formulation.<sup>3</sup>

**INTERACTIONS:**

AGENT	EFFECT	MECHANISM	MANAGEMENT
doxorubicin <sup>3</sup>	increased doxorubicin efficacy and toxicity	decreased clearance of doxorubicin	monitor for increased cardiotoxicity (e.g., congestive heart failure) or consider using docetaxel instead of paclitaxel (docetaxel does not appear to share this same interaction potential) <sup>43</sup>
epirubicin <sup>44-50</sup>	toxicity of both agents may be increased when given concurrently, regardless of which drug is given first; lower neutrophil and platelet nadirs, and slower neutrophil recovery, have been observed	increased levels of epirubicin metabolites, decreased paclitaxel clearance	separate administration by 24 hours if possible
gemcitabine <sup>51</sup>	delayed, moderate, possible; increased gemcitabine efficacy and toxicity	unknown	monitor for gemcitabine toxicity during coadministration
platinum derivatives <sup>15</sup> (e.g., carboplatin, cisplatin)	increased paclitaxel toxicity; paradoxical decreased platelet toxicity from carboplatin <sup>9</sup>	decreased clearance of paclitaxel	paclitaxel should be given first when administering as sequential infusions with either of these drugs
trastuzumab <sup>52</sup>	may increase efficacy of paclitaxel	unknown	preferred method is to give trastuzumab first when administering as sequential infusions
warfarin <sup>51</sup>	delayed, moderate suspected; the anticoagulant effect of warfarin may be increased	decreased warfarin metabolism	monitor coagulation parameters during coadministration or consider use of LMWH during course of chemotherapy <sup>9</sup>

Paclitaxel is a major CYP2C8/9 substrate, therefore drugs that are CYP2C8/9 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin and secobarbital) may decrease the levels/effects of paclitaxel.<sup>3</sup> Likewise, drugs that are CYP2C8/9 inhibitors (e.g., fluconazole, gemfibrozil, ketoconazole, NSAIDs and sulfonamides) may increase the levels/effects of paclitaxel.<sup>3</sup>

Paclitaxel is a major CYP3A4 substrate, therefore drugs that are CYP3A4 inducers (e.g., aminoglutethimide, carbamazepine, nafcillin, phenobarbital and phenytoin) may decrease the levels/effects of paclitaxel.<sup>3</sup> Herbs that are CYP3A4 inducers (e.g., St John's Wort) may also decrease the levels/effects of paclitaxel. Likewise, drugs that are CYP3A4 inhibitors (e.g., azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, propofol, protease inhibitors, quinidine and verapamil) may increase the levels/effects of paclitaxel.<sup>3</sup>

Paclitaxel is also a weak CYP3A4 inducer.<sup>3</sup>

**SUPPLY AND STORAGE:**

**Injection:** Biolyse Pharma supplies paclitaxel as a 6 mg/mL preservative-free solution in single-dose vials of 5 mL, 16.7 mL and 50 mL.<sup>10</sup> Non-medicinal ingredients: dehydrated ethanol 49.7% and Cremophor EL (polyethoxyethylated castor oil).<sup>10</sup> Refrigeration is recommended for long term storage.<sup>10</sup> The potency of paclitaxel is not affected when transported or stored for up to two months at room temperature.<sup>10</sup> Protect vials from light (keep intact vials in their container until use).<sup>10</sup>

Bristol-Myers Squibb supplies paclitaxel as a 6 mg/mL preservative-free solution in multidose vials of 5 mL, 16.7 mL and 50 mL.<sup>2</sup> Non-medicinal ingredients: dehydrated ethanol 49.7% and Cremophor EL (polyethoxylated castor oil) 527 mg.<sup>2</sup> Store vials at room temperature and protect from light (keep intact vials in their container until use).<sup>53</sup>

**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:** Non-polyvinyl (non-PVC) equipment (e.g., polyethylene) is used to minimize leaching. The surfactant,<sup>54</sup> Cremophor EL (polyoxyethylated castor oil), leaches the plasticizer, diethylhexyl phthalate (DEHP), from polyvinyl chloride (PVC) bags and administration sets. Actual hazardous exposure levels to DEHP are not known<sup>55,56</sup>; however, it is hepatotoxic and exposure should be minimized.<sup>57</sup> Use of a plastic syringe to measure a dose is acceptable but drug-syringe contact time should be minimized.

## PARENTERAL ADMINISTRATION:

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

Subcutaneous	not recommended
Intramuscular	not recommended
Direct intravenous	not recommended
<b><i>Intermittent infusion</i></b>	<b><i>in appropriate volume of NS or D5W over 1-3 h</i></b> (range 1-24 h) <ul style="list-style-type: none"> <li>• dilute in non-PVC bags</li> <li>• dilute to final concentration of 0.3-1.2 mg/mL</li> <li>• premedication required to prevent hypersensitivity reactions</li> <li>• administer through non-PVC tubing and a 0.22 micron (non-PVC) in-line filter equipment</li> </ul>
<b><i>Continuous infusion</i></b>	<b><i>as for intermittent infusion except given over 24 h</i></b>
<b><i>Intraperitoneal</i></b>	<b><i>infuse into abdominal cavity as rapidly as possible by gravity</i></b> <sup>58</sup>
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**

<i>Intravenous:</i>	Cycle Length:	
	1 week <sup>3</sup> :	50-80 mg/m <sup>2</sup> over 1-3 hours on day 1
	<b>2 weeks<sup>17</sup>:</b>	<b>when given as a dose-dense regimen with filgrastim (G-CSF) support:</b>
		<b>175 mg/m<sup>2</sup> IV over 3 hours on day 1</b> <b>(total dose per cycle 175 mg/m<sup>2</sup>)</b>
	<b>3 weeks<sup>16,18-23,27,31,33,34</sup>:</b>	<b>135-175 mg/m<sup>2</sup> IV over 3 hours on day 1</b> <b>(total dose per cycle 135-175 mg/m<sup>2</sup>)</b>
	3 weeks <sup>3</sup> :	135 mg/m <sup>2</sup> IV over 24 hours on day 1
	<b>4 weeks<sup>25</sup>:</b>	<b>110 mg/m<sup>2</sup> IV over 1 hour for one dose on days 1 and 8 and 15</b> <b>(total dose per cycle 330 mg/m<sup>2</sup>)</b>
	<b>4 weeks<sup>26,28-30</sup>:</b>	<b>135-175 mg/m<sup>2</sup> IV over 3 hours on day 1</b> <b>(total dose per cycle 135-175 mg/m<sup>2</sup>)</b>

<i>Suggested premedication regimen<sup>16-34</sup>:</i>	any:	45 minutes before: dexamethasone 20 mg IV 30 minutes before: diphenhydramine 50 mg IV; ranitidine 50 mg IV
		In the event of a treatment delay (e.g., admixture is unavailable), additional doses are required. <sup>10</sup>

*Concurrent radiation:* generally not administered concurrently due to additive toxicity

*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<sup>3</sup>:* no adjustment required

*Dosage in hepatic failure<sup>3,15</sup>:*

<b>Suggested guidelines for first course; subsequent courses should be based on individual tolerance</b>			
<b>paclitaxel 24 h infusion:</b>			
<b>ALT</b>		<b>bilirubin</b>	<b>dose</b>
<2 X ULN	and	<26 µmol/L	135 mg/m <sup>2</sup>
2 to <10 X ULN	and	<26 µmol/L	100 mg/m <sup>2</sup>
<10 x ULN	and	27-128 µmol/L	50 mg/m <sup>2</sup>
≥10 x ULN	or	>128 µmol/L	not recommended
<b>paclitaxel 3 h infusion:</b>			
<b>ALT</b>		<b>bilirubin</b>	<b>dose</b>
<10 X ULN	and	<1.25 x ULN	175 mg/m <sup>2</sup>
<10 X ULN	and	1.26-2.0 x ULN	135 mg/m <sup>2</sup>
<10 X ULN	and	2.01-5.0 x ULN	90 mg/m <sup>2</sup>
≥10 x ULN	or	>5.0 x ULN	not recommended

*Dosage in dialysis:* *hemodialysis:* no significant removal by hemodialysis; **no dose adjustment required; may be administered before or after hemodialysis session<sup>3</sup>**

*chronic ambulatory peritoneal dialysis (CAPD):* no significant removal by peritoneal dialysis; **no dose adjustment required<sup>59</sup>**

**Children:**

<i>Intravenous</i> <sup>60-63</sup> :	Cycle Length:	
	3 weeks:	350 mg/m <sup>2</sup>
<i>Suggested premedication regimen</i> <sup>64</sup> :	any:	12 and 6 hours before: dexamethasone 0.15 mg/kg (up to 20 mg) po <b>OR</b> 30 minutes before: 0.15 mg/kg (up to 20 mg) IV 30-60 minutes before: diphenhydramine 1 mg/kg (up to 50 mg) IV; ranitidine 1 mg/kg (up to 50 mg) IV
		In the event of a treatment delay (e.g., admixture is not available), additional doses are required.

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