DRUG NAME: Docetaxel

SYNONYM(S): RP56976

COMMON TRADE NAME(S): TAXOTERE®, DOCEFREZ®

CLASSIFICATION: mitotic inhibitor

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

MECHANISM OF ACTION:

Docetaxel is a taxane derivative similar to paclitaxel. Docetaxel binds to tubulin, the protein component of microtubules, and simultaneously promotes assembly and inhibits disassembly of them. Stabilization of microtubules leads to inhibition of cell division (mitosis) and tumour proliferation, resulting in cell death. Both docetaxel and paclitaxel bind to the same microtubule site.[1] Docetaxel is approximately 2 times as potent as paclitaxel and at least 5 times more potent against paclitaxel-resistant cells.[2] Although some reports indicate a cross-reactivity rate of 90% between docetaxel and paclitaxel, others suggest it does not occur consistently.[3,4] Docetaxel is cell cycle phase-specific for the G_2/M phase.[1,5] Docetaxel is a radiation-sensitizing agent[2] and an immunosuppressant.[6]

PHARMACOKINETICS:

Oral Absorption	oral bioavailability of IV solution 8%[2]	
Distribution	time to peak concentration 1 to 2 h; widely distributed[2]	
	cross blood brain barrier?	yes; very low levels
	volume of distribution	113 L
	plasma protein binding	>95%
Metabolism	primarily hepatic via CYP 3A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	1 major, 3 minor (names unknown)[2]
Excretion	primarily in feces[7]	
	urine	unchanged (5-6%)[2,8]
	feces	80% excreted during first 48 h as major metabolite; 8% as unchanged drug[7]
	terminal half life	11 h
	clearance	21 L/h/m²; decreased by 27% in mild to moderate liver impairment
Sex	no difference	
Elderly	no difference	
Children[9,10]	clearance 17-21 L/h/m²	
Ethnicity	no difference	

Adapted from standard reference[1] unless specified otherwise.

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USES:

Primary uses:
*Breast cancer
*Lung cancer, non-small cell
*Ovarian cancer
*Prostate cancer
*Head and neck cancer

*Health Canada approved indication

Other uses:
Sarcoma, Ewing[9]
Neuroblastoma[9]
Osteosarcoma[9]

SPECIAL PRECAUTIONS:

Contraindications:
- history of severe hypersensitivity reaction to docetaxel.[1]

Caution:
- patients with ***preexisting severe fluid retention*** should be closely monitored for possible exacerbation of effusions[1]
- patients with ***preexisting liver impairment*** are at a higher risk of developing severe adverse reactions[1,11]

Carcinogenicity: no information found

Mutagenicity: not mutagenic in Ames test or mammalian *in vitro* mutation test. Docetaxel is clastogenic in mammalian *in vivo* micronucleus test but is not clastogenic in mammalian *in vitro* chromosome test.[1]

Fertility: Testicular atrophy or degeneration was observed in animal studies.[9]

Pregnancy: FDA Pregnancy Category D.[3,8,9] 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). Docetaxel has been shown to be embryotoxic and fetotoxic in animal studies, causing intrauterine mortality, reduced fetal weight and delayed fetal ossification.[1]

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

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.[12,13] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (90%, severe 9%)
	febrile neutropenia (11-25%)
	leucopenia (96%, severe 32%)
	neutropenia (96%, severe 75%); nadir 7 days, duration of severe neutropenia 7 days
	thrombocytopenia (8%, severe <1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	dysrhythmia (2%, severe <1%)
	fluid retention, with premedication (64%, severe 7%); see paragraph following **Side Effects** table
	fluid retention, without premedication (82%, severe 22%); see paragraph following **Side Effects** table
	myocardial infarction
	venous thromboembolic event
ear and labyrinth	hearing impairment
eye	lacrimation (5-64%)[1,2]; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[14]
	colitis[1,15]
	diarrhea (39%, severe 5%)
	dysgeusia (6-14%, severe <1%)[1,8]
	ileus
	intestinal obstruction
	nausea (39%, severe 4%)
	stomatitis (42%, severe 6%)
	vomiting (22%, severe 3%)
general disorders and administration site conditions	*extravasation hazard:* irritant[16]
	fatigue (25%, severe 5%)
	fever (32%, severe 2%)
	injection site reaction (4-6%)
immune system	***hypersensitivity reactions*** (17-21%, severe 4%); see paragraph following **Side Effects** table
infections and infestations	infection, including sepsis and pneumonia (6-22%, severe 2%)
injury, poisoning, and procedural complications	radiation recall reaction[1,17]
investigations	alkaline phosphatase, elevated (4-7%)[8]
	ALT/AST, elevated (<5%)
	bilirubin, elevated (6-9%, severe 2%)[1,8]
metabolism and nutrition	dehydration (5%, severe <1%)
musculoskeletal and connective tissue	arthralgia (9%, severe <1%)
	myalgia (19%, severe 2%)
neoplasms	leukemia, acute myeloid
	myelodysplastic syndrome
nervous system	peripheral motor neuropathy (14%, severe 4%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	peripheral sensory neuropathy (49%, severe 4%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal (see paragraph after Side Effects table)	cough[18] (9%)
	dyspnea[18,19] (9-15%, severe <1%)
	epistaxis[18,19] (5-17%)
	pleural effusion (9%)[2,20]
	pneumonitis, interstitial [20-22]
	pulmonary edema (<1%)[18,23]
	sore throat[18] (7%, severe <1%)
skin and subcutaneous tissue	***alopecia*** (76-85%, severe <1%); see paragraph following **Side Effects** table
	cutaneous reactions (48%, severe 5%); see paragraph following **Side Effects** table
	nail changes (31%, severe 3%); see paragraph following **Side Effects** table
	palmar-plantar erythrodysesthesia (8%)
	rash with pruritus (48%, severe 5%)
vascular	hypertension (2%)
	hypotension (3%, severe <1%)

Adapted from standard reference[1] unless specified otherwise.

Pre- and post-treatment administration of dexamethasone is recommended to decrease the frequency and severity of fluid retention and hypersensitivity reactions.[1] Premedication with 3 doses of dexamethasone prior to each docetaxel infusion is a standard for both the 3-weekly and weekly docetaxel regimens.[1,24,25] If dexamethasone has not been taken prior to treatment, and if treatment delay is not possible, a single 8 mg PO/IV dose of dexamethasone, along with diphenhydramine 50 mg IV, may be given 30 minutes prior to docetaxel.[24,25] A single dexamethasone dose has not been shown to reduce the incidence and severity of fluid retention, but is only an attempt to ameliorate hypersensitivity reactions. The patient should then be instructed to take dexamethasone 8 mg PO twice a day for two days.[26] See Dosage Guidelines for premedication regimens.

Fluid retention due to docetaxel may be caused by increased capillary permeability rather than hypoalbuminemia or cardiac, hepatic or renal damage. The abnormal capillary membrane allows an accumulation of proteins in the interstitial space.[27] Symptoms include progressive peripheral edema, pleural effusion, ascites, pericardial effusion and weight gain.[1] Severe symptoms include poorly tolerated peripheral edema, generalized edema, dyspnea at rest, cardiac tamponade, pleural effusions requiring urgent drainage or pronounced abdominal distention.[2,27] Fluid retention usually begins in the lower extremities and may become generalized with a median weight gain of 2 kg. It is cumulative in incidence and severity; the median cumulative dose to onset of moderate or severe fluid retention is 819 mg/m². Fluid retention is not accompanied with dehydration, oliguria or hypotension, and is slowly reversible after docetaxel treatment is stopped. Patients must receive a minimum of 3 doses of dexamethasone before each treatment to reduce the incidence and severity of fluid retention.[1]

Hypersensitivity reactions can occur with docetaxel.[1] More than one mechanism may account for the reactions, and mechanisms may differ between individuals. Suggested mechanisms include: IgE-mediated, non-IgE-mediated, histamine-mediated and tryptase-mediated mechanisms.[28] Minor reactions are characterized by flushing, rash (with or without pruritus), chest tightness, back pain, dyspnea, drug fever, or chills. Severe reactions include hypotension, bronchospasm, generalized rash/erythema, or very rarely, anaphylaxis.[1] The majority of hypersensitivity reactions develop during the first or second infusion, within the first few minutes following initiation of the infusion.[1,28] Hypersensitivity reactions are reported with a higher incidence in patients receiving docetaxel in the second line

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setting, possibly due to immunological stimulation caused by other drugs used in the adjuvant or first line setting.[29] The hypersensitivity response to docetaxel may also be affected by the sequence of infusions within the regimen. For example, hypersensitivity reactions have been shown to be reduced when docetaxel is sequentially infused after cyclophosphamide, possibly due to an immunosuppressive effect of cyclophosphamide.[30] The presence of comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, hypertension and coronary artery disease) are not associated with the development of reactions to docetaxel.[29] Premedication with corticosteroids and antihistamines reduces the incidence and severity of reactions. Serious reactions are reduced from 30% to 2% when dexamethasone is used as premedication and dosed at 8 mg twice a day for 3 days, starting one day before administration.[1,28] All reactions resolve with discontinuation of treatment followed by appropriate therapy.[1] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Rechallenge after severe hypersensitivity reaction:
Patients who have demonstrated hypersensitivity reactions to docetaxel are able to be retreated, even on the same day.[28,31] Most patients who experience mild-to-moderate reactions tolerate re-administration of docetaxel using a slower infusion rate after all symptoms have resolved.[32,33] Patients who experience severe hypersensitivity reactions should not be rechallenged with docetaxel.[1] However, if there is no alternative, or if the patient develops another reaction after rechallenge, desensitization protocols have been used successfully and may be considered.[28,29,31,34,35] Sodium cromoglycate and ketotifen have been used for prophylaxis in patients who developed hypersensitivity reactions to taxanes.[36] The decision to rechallenge should be left to the discretion of the prescribing physician.[33]

Cutaneous reactions commonly present as a rash, with or without pruritus, on the hands, feet, arms, face or thorax. Eruptions can occur within one week, but resolve before the next infusion. Severe cutaneous reactions have been reported and include rare cases of lupus erythematosus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes. Docetaxel does not have to be discontinued for minor reactions such as flushing or localized skin reactions, but may require a dose reduction for severe or cumulative cutaneous reactions.[1,37,38] Discontinuing docetaxel should be considered in patients experiencing severe reactions despite dose adjustments.[2]

Nail changes are characterized by hyperpigmentation, splinter hemorrhage, subungual hematoma and hyperkeratosis, orange discoloration, Beau-Reil lines (which indicate the cessation of nail growth), and acute paronychia. Some changes are cosmetic and asymptomatic, whereas others can be accompanied by discomfort or pain. Changes are usually transient and disappear with treatment withdrawal, although there are reports of persistent changes. Loosening or loss of nails (onycholysis) occurs in 2-22%. Nail bed infections may be a complication and the application of topical antibiotics or antifungals may be necessary. Applying the principle of cold-induced vasoconstriction by wearing frozen gloves on the hands during treatment may reduce the incidence of nail and skin toxicity. In one study, overall incidence of nail toxicity was reduced with frozen glove treatment from 51% to 11%, and the incidence of grade 2 toxicity (onycholysis) was reduced from 22% to 0%. Additionally, median time of occurrence of nail toxicity was delayed to 106 days with frozen glove treatment as opposed to 58 days without.[39]

Neuropathy is related to the cumulative dose of docetaxel and can potentially limit the number of cycles that can be given.[2,25] Mild to moderate sensory neuropathy has been reported in patients treated with cumulative IV doses between 50-720 mg/m^2; however, the onset and severity are highly variable among individuals.[2,13] Severe sensory neuropathic symptoms include paresthesias, dysesthesias and pain. The median time to resolution of symptoms is 9 weeks; however, neuropathic symptoms can persist in milder form for many months or permanently.[2,13] Severe peripheral motor neuropathy is rare and is characterized by distal extremity weakness.[2] Many patients describe generalized decline in exercise tolerance which may be in part due to mild motor neuropathy.[13] Dose reductions should be considered if severe neuropathic symptoms develop; treatment may need to be discontinued if symptoms do not resolve following a dose reduction.[1,2]

Hair loss, including on the head, eyebrows, eyelashes, pubic area, and underarm, occurs in most patients.[40] Alopecia has a sudden onset, and occurs 14-21 days after treatment has begun.[41] Hair should grow back once treatment has been completed; however, cases of poor hair re-growth and/or persistent hair loss have been reported.[40,42-44] Reports suggest some patients may experience prolonged hair loss lasting beyond 24 months, and possibly irreversibly.[40,42,43]

Lacrimation or tearing/watery eyes, with or without conjunctivitis has been reported. Obstruction of the lacrimal ducts may be involved. Symptoms include transient, reversible, visual disturbances (flashes, flashing lights,

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defective vision) typically in association with hypersensitivity reactions.[1] Mean onset of tearing with weekly docetaxel is 2 months, with a median cumulative dose of 497 mg (range 140-843 mg). Mean onset of tearing with 3 weekly docetaxel is 3 months, with a median cumulative dose of 420 mg (range 162-1438 mg).[2] Treatment with topical antibiotics and corticosteroids resolves symptoms.[2] Some patients may benefit from stenting of the lacrimal duct if fibrosis is observed.[2,13]

Pulmonary toxicity has been associated with docetaxel**,** including acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, lung infiltration, pulmonary fibrosis, respiratory failure, radiation recall phenomena, as well as radiation pneumonitis with concomitant radiotherapy.[18] Pulmonary toxicity typically presents with fever, cough, dyspnea, and diffuse lung infiltrates. In some patients, symptoms progress rapidly and result in prolonged respiratory failure requiring mechanical ventilation. Fatal outcomes have been reported. The mechanism of pulmonary toxicity is not clear.[21,23,45] Time to onset of toxicity may be delayed; cases have been reported variously from 8-14 days after receiving cycle 2 or 3 of treatment and up to 21 days after cycle 6.[21,22,46] Once toxicity occurs, consider reducing or withholding docetaxel and initiate corticosteroid treatment as indicated.[20,22]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
capecitabine[1]	no pharmacokinetic interaction with docetaxel		
carboplatin[47,48]	no pharmacokinetic interaction with docetaxel		
cyclophosphamide[1]	no pharmacokinetic interaction with docetaxel		
dexamethasone[1]	dexamethasone does not affect protein binding of docetaxel	both drugs are highly protein bound	
digoxin[1]	docetaxel does not affect protein binding of digoxin	both drugs are highly protein bound	
disulfiram[48]	development of acute and severe alcohol intolerance reactions	inhibition of aldehyde dehydrogenase by disulfiram, leading to development of toxic metabolites of ethanol (found in the supplied diluent)	avoid disulfiram concurrently with docetaxel administration
diphenhydramine[1]	diphenhydramine does not affect protein binding of docetaxel	both drugs are highly protein bound	
doxorubicin[1]	no pharmacokinetic interaction with docetaxel		
erythromycin[1]	erythromycin does not affect protein binding of docetaxel	both drugs are highly protein bound	
fluorouracil[47]	no pharmacokinetic interaction with docetaxel		
irinotecan[47]	no pharmacokinetic interaction with docetaxel		
ketoconazole[1,48,49]	docetaxel AUC increased 2 fold; increased risk or severity of docetaxel toxicity	inhibition of CYP 3A4 by ketoconazole, reducing docetaxel clearance by 49%	avoid concurrent use if possible; if unavoidable, consider reducing docetaxel dose by 50%

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AGENT	EFFECT	MECHANISM	MANAGEMENT
metronidazole and derivatives[48]	possible 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 the supplied diluent)	avoid metronidazole or its derivatives concurrently with docetaxel administration
netupitant[50-52]	docetaxel AUC increased by 35%, Cmax by 49%	inhibition of CYP 3A4 by netupitant	monitor for increased docetaxel toxicity[50]; consider alternate NK_1 antagonist
phenytoin[1]	phenytoin does not affect protein binding of docetaxel	both drugs are highly protein bound	
prednisone[1]	no effect on pharmacokinetics of docetaxel		
propafenone[1]	propafenone does not affect protein binding of docetaxel	both drugs are highly protein bound	
propranolol[1]	propranolol does not affect protein binding of docetaxel	both drugs are highly protein bound	
ritonavir[1,48]	increased risk of hematologic toxicity from docetaxel	inhibition of CYP 3A4 by ritonavir, increased docetaxel exposure	avoid concurrent use if possible; if unavoidable, consider reducing docetaxel dose by 50%
salicylate[1]	salicylates do not affect protein binding of docetaxel	both drugs are highly protein bound	
sodium valproate[1]	sodium valproate does not affect protein binding of docetaxel	both drugs are highly protein bound	
sorafenib[48,49]	increased docetaxel toxicity	unknown	monitor for increased docetaxel toxicity during concurrent use
sulfamethoxazole[1]	sylfamethoxazole does not affect protein binding of docetaxel	both drugs are highly protein bound	
vaccines, live[48]	risk of enhanced viral replication; may increase the risk of disseminated disease	decreased immune response allows live vaccine to produce infection	avoid vaccination with live vaccines during treatment
vinorelbine[47]	no pharmacokinetic interaction with docetaxel		

Docetaxel is a **substrate** for CYP 3A4.[9] Strong inhibitors and inducers of this enzyme may alter docetaxel pharmacokinetics. Inhibitors of CYP 3A4 may increase the plasma concentration and pharmacologic effect of docetaxel, elevating the risk or severity of docetaxel-related toxicity. Avoid concurrent use if possible. Consider a docetaxel dose reduction of 50% if a strong CYP 3A4 inhibitor cannot be avoided.[1] Grapefruit or grapefruit juice may inhibit CYP 3A4 metabolism in the intestinal wall and liver, and theoretically may increase the plasma level of docetaxel; clinical significance of this interaction is unknown.[53,54] Inducers of CYP 3A4 may increase the metabolism of docetaxel, resulting in a decreased pharmacologic effect of docetaxel, requiring dose titration for therapeutic effect.[55]

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Docetaxel is a **substrate** for the transport protein P-glycoprotein (P-gp).[1,2,56] Inhibitors of P-gp may increase the exposure to docetaxel, elevating the risk or severity of docetaxel-related toxicity. Inducers of P-gp may decrease the pharmacologic effect of docetaxel, requiring dose titration for therapeutic effect.[56]

SUPPLY AND STORAGE:

***Injection*:**
Hospira Healthcare Corporation supplies docetaxel as a 20 mg single dose vial, and 80 mg or 160 mg multi-dose vials in a concentration of 10 mg/mL. Store at room temperature. Protect from light.
Non-medicinal ingredients: 0.23 mL ethanol anhydrous per 1 mL of solution.[1]

sanofi-aventis Canada Inc. supplies docetaxel as 20 mg and 80 mg vials in a concentration of 40 mg/mL. Withdraw and inject the entire contents of the solvent into the corresponding docetaxel concentrate vial to give a premix solution concentration of 10 mg/mL. Store at room temperature. Protect from light.
Non-medicinal ingredients: 20 mg vial contains 1.98 mL of 13% ethanol in water for injection; 80 mg vial contains 7.33 mL of 13% ethanol in water for injection.[6]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Additional information:
- Concentrated solution must be diluted prior to IV infusion.[1]
- To prevent extraction of plasticizer DEHP from container, prepare solutions in non-DEHP containers and administer using non-DEHP administration sets.[1]
- sanofi-aventis brand: both docetaxel and diluent vials may contain overfill to ensure the minimal extractable premix volume[6]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	not used due to dilution required prior to administration[1]
Intermittent infusion	***over 1 h*** (use non-DEHP administration sets)[1,57-82] • patient must receive dexamethasone before each treatment[1] • observe patient closely for hypersensitivity reactions during the first few minutes of the infusion, particularly during the first and second infusions[1]
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found

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BC Cancer administration guideline noted in ***bold***, ***italics***

Intra-arterial	no information found
Intravesical[83-85]	induction doses of 75 mg in 100 mL NS have been used weekly for 6 weeks, followed by monthly maintenance doses to 1 year; solutions are retained for 1-2 h after instillation

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*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks[1,57-82]***:	***75-100 mg/m^2 IV for one dose on day 1*** (total dose per cycle 75-100 mg/m^2)
	***8 weeks[86-89]*:**	***36 mg/m² IV for one dose on days 1, 8, 15, 22, 29, 36*** (total dose per cycle 216 mg/m²)
	6 weeks[1]:	30 mg/m² IV for one dose on days 1, 8, 15, 22 and 29 (total dose per cycle 150 mg/m²)
Premedication regimen:	***3 weeks[1]***:	***dexamethasone 8 mg PO twice a day for 3 consecutive days, starting one day prior to each docetaxel infusion*** (total dose per cycle 48 mg)
	weekly[24,25]:	***dexamethasone 8 mg PO for 1 dose given 1 hour before infusion***
	3 weeks[1]:	dexamethasone 8 mg PO for 3 doses, starting 12 hours, 3 hours and 1 hour before each docetaxel infusion (total dose per cycle 24 mg)
	weekly[24,25]:	dexamethasone 8 mg PO every 12 hours for 3 doses starting the evening before docetaxel infusion
Concurrent radiation:	1 week[5,86]:	investigational, 20 mg/m² IV for one dose on day 1
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no information found	

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Dosage in hepatic failure:

3 weeks[1,6]:

Alkaline Phosphatase		AST +/or ALT		Bilirubin	Dose
<2.5xULN	and	<1.5xULN	--	--	100 mg/m²
2.5-6xULN	and	1.5-3.5xULN	--	--	75 mg/m²
>6xULN	and	>3.5xULN	or	>ULN	avoid use

ULN = upper limit of normal

weekly: no information found

Dosage in dialysis: hemodialysis: no significant removal; no dose adjustment required, may be administered before or after hemodialysis[90,91]

Children:

Intravenous: safety and effectiveness not established in children[1]; 100-125 mg IV every 3 weeks has been given[10]

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