Drug Monograph

A - Drug Name

DOCEtaxel

COMMON TRADE NAME(S): Taxotere®

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B - Mechanism of Action and Pharmacokinetics

Docetaxel acts by disrupting the microtubular network in cells that is essential for cell division. It promotes the assembly of tubulin into stable microtubules, while simultaneously inhibiting their disassembly. This leads to the stabilization of microtubules, resulting in the inhibition of mitosis in cells.

Distribution	Dose-independent pharmacokinetics; disposition is triphasic following 70-115 mg/m^2. Well distributed to various organs and tissues.	
	Cross blood brain barrier?	No
	PPB	> 95 %
Metabolism	Docetaxel is metabolized primarily by the cytochrome P450-3A enzymes.	
	Active metabolites	no
	Inactive metabolites	yes
Elimination	Docetaxel is mainly excreted into feces via the bile.	
	Urine	6%

Feces	75%, mostly as inactive metabolites
Half-life	11 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Breast cancer
- Non-small cell lung cancer
- Ovarian cancer
- Prostate cancer
- Head and neck cancer

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Gastroesophageal cancer
- Bladder/urothelial cancer
- Gynecological sarcoma
- Soft tissue sarcoma

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: Irritant

The following table contains adverse effects reported mainly in docetaxel monotherapy for breast, lung and ovarian cancer. Severe or life-threatening adverse events from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (2%)	I
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (<1%)	I
	Hypertension (2%)	I
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (76%) (<1% severe) (rarely permanent)	E
	Hand-foot syndrome (rare)	E
	Nail disorder (31%) (severe 3%)	E D
	Other - Acute generalized exanthematous pustulosis (rare)	E
	Radiation recall reaction and injection site recall reaction	E
	Rash (48%) (5% severe)	E D
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Colitis (rare, may be severe)	E
	Diarrhea (39%) (may be severe)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Mucositis (42%) (severe 6%)	E
	Nausea, vomiting (39%)	I
General	Fatigue (62%) (severe 13%)	E
	Fluid retention (47%) (with pre-medication; severe 7%)	I D
Hematological	Disseminated intravascular coagulation (rare)	E
	Myelosuppression ± infection, bleeding (75%) (severe)	E
Hepatobiliary	↑ LFTs (<5%) (may be severe)	E
Hypersensitivity	Hypersensitivity (21%) (severe 4%)	I

Injection site	Injection site reaction (6%)	I
Metabolic / Endocrine	Tumor lysis syndrome (rare)	I
Musculoskeletal	Musculoskeletal pain (19%)	E
Neoplastic	Secondary malignancy (AML, MDS, non-Hodgkin lymphoma, renal)	D
Nervous System	Cognitive disturbance (rare)	E
	Myositis (rare)	E
	Neuropathy (49%) (severe 4%)	E D
	Seizure (rare)	E
Ophthalmic	Cystoid macular edema	E
	Eye disorders (transient visual disturbance - rare)	E
	Other (lacrimal duct obstruction)	E
	Watering eyes	E
Renal	Renal failure (rare, concurrent nephrotoxic drugs)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (rare)	E
	Dyspnea (5%) (with prednisone in prostate cancer)	E
	Pneumonitis (rare, also reported in combination with radiotherapy)	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 side effects for DOCEtaxel include alopecia, myelosuppression, fatigue, neuropathy, skin/nail effects, fluid retention, mucositis, diarrhea, nausea/vomiting and hypersensitivity.

The major dose-limiting adverse effect of docetaxel is **myelosuppression**. Neutropenia is reversible and not cumulative. Febrile neutropenia occurred in 11%. Infectious episodes were fatal in 2% of patients. Patients with neutropenia are particularly at risk of developing gastrointestinal complications.

Severe **hypersensitivity** reactions characterized by hypotension, bronchospasm or generalized rash/erythema may occur within a few minutes of docetaxel infusions and may potentially be fatal. All patients receiving docetaxel should be pre-medicated with oral dexamethasone and should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Patients who are hypersensitive to paclitaxel are at an increased risk. Depending on the severity of the symptoms, appropriate treatment for sensitivity reactions associated with docetaxel may include

a decrease in the rate of the infusion, immediate interruption of the infusion, IV administration of diphenhydramine with or without dexamethasone and/or epinephrine as needed, pre-medication with an oral or IV antihistamine prior to the next cycle of docetaxel, or discontinuance of docetaxel therapy. Patients who experience severe hypersensitivity reactions should not be re-challenged.

Diarrhea, nausea and vomiting are common, may be severe and may be associated with electrolyte disturbances. Fatal cases of enterocolitis have been reported; it can develop at any time and can lead to death as early as on the first day of onset.

Docetaxel-induced **fluid retention** is cumulative in severity and incidence, generally reversible but may be severe with ascites, pleural or pericardial effusions. Premedication decreases the severity of fluid retention, and all patients should receive premedication. Use with caution in patients with existing effusions and ascites.

Cutaneous reactions are dose-dependent and cumulative, characterized by a rash, including localized eruptions mainly on feet and hands (palmar-plantar dysesthesia), but also on arms, face or thorax, and may be associated with pruritus. Eruptions generally occur within 1 week following the docetaxel infusion, and usually resolve before the next infusion. Therapy for erythrodysesthesia has generally been symptomatic. Severe nail disorder (cumulative) may occur. Alopecia is dose-related but may rarely be permanent.

Musculoskeletal manifestations usually are transient, occurring within a few days after docetaxel administration lasting about 4 days.

Docetaxel can cause a dose-related reversible sensory **neuropathy.** Severe symptoms are less common but require dose modifications.

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

Weekly docetaxel regimens have been tested, but have not been approved by Health Canada. Weekly regimens appear to be associated with a slightly different toxicity profile.

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E - Dosing

Refer 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):

- Dexamethasone* 8 mg PO BID for 3 days, starting 1-day pre-infusion†

An alternative for patients with prostate cancer being treated with prednisone:

- Dexamethasone* 8 mg PO 12 hours, 3 hours, and 1 hour pre-infusion.

* Do not discontinue dexamethasone, even in the absence of an IR, due to the benefits on other adverse effects (e.g. pain and edema).

† Dexamethasone 10-20 mg IV can be given if patient forgot to take oral doses.

Patients should not be treated until they have recovered from prior toxicity and have acceptable blood counts (ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L).

Patients with head and neck cancer are at increased risk of febrile neutropenia and prophylactic antibiotics should be used (i.e. oral fluoroquinolone for 10 days starting on day 5).

Refer to the 2016 CCO Recommendations on G-CSF (prophylaxis of febrile neutropenia in adult patients undergoing systemic treatment).

Adults:

Monotherapy - *Prostate cancer (with prednisone)*:

Intravenous: 75 mg/m² administered as an 1 hour infusion Every 3 weeks

Monotherapy - *All other disease sites:*

Intravenous: 75 to 100* mg/m² administered as an 1 hour infusion Every 3 weeks

* Refer to the regimen monographs for dosing in specific disease sites

Combination:

Intravenous: 75 mg/m² administered as an 1 hour infusion Every 3 weeks

Dosage with Toxicity:

Toxicity (worst in previous cycle)	Modification*		
(Previous dose)	**100mg/m^2**	**75mg/m^2**	**% of previous dose**
Febrile neutropenia / Grade 4 ANC ≥ 7 d	75mg/m^2 (or G-CSF)	60mg/m^2 (or G-CSF)	75%
Grade 3 skin/ neuro/ major organ/ non-hematologic toxicity	75mg/m^2	60mg/m^2	75%
Any occurrence of cystoid macular edema	Hold and investigate; refer patient promptly an ophthalmic examination. Discontinue if confirmed.		
Grade 4 skin/ neuro/ major organ/ non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction OR Any Severe Cutaneous Adverse Reactions (SCARs) (e.g. Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute generalized exanthematous pustulosis (AGEP))	Discontinue	Discontinue	Discontinue
* Do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and non-hematologic/organ toxicity ≤ 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, replace 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 symptoms 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:

Patients with hepatic impairment have a higher risk of severe adverse effects, including fatal gastrointestinal hemorrhage, sepsis and myelosuppression.

Bilirubin		AST and/or ALT		Alkaline Phosphatase	Docetaxel dose
> ULN	AND	Any	AND	Any	Do not treat. Discontinue if treatment already started.
Any	AND	> 1.5 X ULN	AND	> 2.5 x ULN	

Dosage with Renal Impairment:

No adjustment required.

Dosage in the elderly:

No adjustment required, but caution should be exercised in elderly patients with poor performance status who are receiving docetaxel. Patients over the age of 60 years appear to have increased toxicity when docetaxel is used in combination with capecitabine, as do patients treated with docetaxel for prostate cancer (>65 years).

Children:

Safety and effectiveness in children have not been established.

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F - Administration Guidelines

- Refer to the respective product monographs for preparation instructions. Mix in 250mL D5W or NS to a maximum concentration of 0.3-0.74 mg/mL. For doses over 200 mg, use a larger volume of the infusion vehicle so the maximum concentration is not exceeded.
- Infuse through main IV line over 1 hour.
- 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.
- To minimize hypersensitivity reactions, docetaxel infusion should be started at a slow rate, then increased incrementally to planned rate.
- Monitor patient for signs of alcohol intoxication (due to alcohol content in formulation) during and after the infusion. Slowing the infusion rate during administration may help resolve symptoms.
- Injection site recall reactions (recurrence of skin reaction at a previous extravasation site after docetaxel is administered at a different site) have been observed.

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 who have a history of hypersensitivity reactions to docetaxel, to other drugs formulated with polysorbate 80 or polyethylene glycol 300, or to any components of the formulation
- Patients with baseline neutrophil counts of < 1.5 x 10^9/L
- Patients with severe liver impairment

Other Warnings/Precautions:

- Use with caution in patients with pre-existing effusions or ascites.
- Use with caution in patients who are hypersensitive to paclitaxel. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a potentially fatal hypersensitivity reaction to docetaxel.
- Docetaxel contains ethanol (refer to respective product monographs) and may cause drowsiness. Patients should be cautioned regarding driving and the use of machinery immediately after receiving the infusion. Ethanol may be harmful to patients at risk of adverse effects such as those with alcoholism, liver disease, epilepsy and children. Cases of alcohol intoxication have been reported.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Crosses placental barrier: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Mutagenicity: Yes
- Genotoxicity: Yes
  Docetaxel is **contraindicated** for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **6 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **3 months** after the last dose.
- Breastfeeding: Contraindicated
  Breastfeeding is **contraindicated** during treatment and for **1 week** after the last dose.

- Fertility effects:
  Yes; especially for male fertility

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H - Interactions

Docetaxel is also a substrate of p-glycoprotein. Inducers and inhibitors of p-glycoprotein may potentially affect docetaxel efficacy or increase docetaxel toxicity respectively.

No pharmacokinetic interaction was observed with docetaxel, when used with doxorubicin and/or cyclophosphamide, with capecitabine, or with daily prednisone and dexamethasone premedication.

Highly protein-bound drugs, such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect docetaxel protein binding. Docetaxel did not affect the protein binding of digoxin.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ docetaxel exposure (up to 2.2 x) and toxicity	↓ metabolism of docetaxel	Avoid concomitant use; consider docetaxel dose ↓ if must use together (50% for strong inhibitors)
Substrates or inducers of CYP3A4 (i.e. cyclosporine, nifedipine, troleandomycin, orphenadrine, testosterone, midazolam)		Alteration of docetaxel pharmacokinetics	Caution
Dronedarone	↑ docetaxel severe toxicities (case report)	Inhibits P-gp and CYP3A4; delayed clearance of docetaxel	Avoid combination
Epirubicin	↑ systemic exposure to epirubicin or its metabolites. May be schedule dependent.	Docetaxel (or polysorbate 80) is suggested to interact with epirubicin metabolism and/or excretion	Caution if used in combination; give epirubicin first

Sorafenib	↑ docetaxel exposure	Unknown	Caution; monitor for toxicity
CNS depressants (e.g. benzodiazepines, opioids)	↑ risk of CNS depression	Additive due to ethanol in docetaxel formulations	Caution; monitor for intoxication during and after infusions

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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, including nadir counts	Baseline and before each dose
Liver function tests	Baseline and before each cycle
Clinical toxicity assessment of infection, bleeding, neurotoxicity, fluid retention, hypersensitivity, lethargy, cutaneous reactions, thromboembolism, cardiovascular, musculoskeletal pain, secondary malignancies, ophthalmic, GI, respiratory effects or enterocolitis especially in the setting of neutropenia	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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May 2024 Updated Adverse effects, Dose modifications, Pregnancy/lactation, and Monitoring sections

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L - Disclaimer

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