DOCEtaxel

COMMON TRADE NAME(S):  Taxotere®

**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**

Linear, dose dependent pharmacokinetics. Exposure is dose proportional and disposition is triphasic following 70-115 mg/m². Highest concentrations were found in the liver, bile and intestine.

- 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%
C - Indications and Status

Health Canada Approvals:

- Locally advanced or metastatic breast carcinoma as 1) a single agent; 2) in combination with capecitabine after failure of prior anthracycline chemotherapy; 3) in combination with doxorubicin as first-line therapy, for patients with potentially life-threatening disease (such as visceral or lung metastatic disease)
- Locally advanced or metastatic non-small cell lung cancer in monotherapy or in combination with platinum agents
- Recurrent and/or metastatic squamous cell carcinoma of the head and neck as monotherapy after the failure of prior chemotherapy
- Metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy
- Androgen-independent (hormone-refractory) metastatic prostate cancer in combination with prednisone (or prednisolone)
- Adjuvant treatment in patients with operable node-positive breast cancer in combination with doxorubicin and cyclophosphamide

Other Uses:

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

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.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Arrhythmia (2%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Arterial thromboembolism (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity (&lt;1%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Hypertension (2%)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism (rare)</td>
<td>E</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Alopecia (76%) (rarely permanent)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Hand-foot syndrome (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Nail disorder (31%) (severe 3%)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Radiation recall reaction and injection site recall reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash (48%) (5% severe)</td>
<td>E</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Colitis (rare, may be severe)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Diarrhea (39%) (may be severe)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>GI obstruction (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>GI perforation (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Mucositis (42%) (severe 6%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting (39%)</td>
<td>I</td>
</tr>
<tr>
<td>General</td>
<td>Fatigue (62%) (severe 13%)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Fluid retention (47%) (with pre-medication; severe 7%)</td>
<td>I D</td>
</tr>
<tr>
<td>Hematological</td>
<td>Disseminated intravascular coagulation (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Myelosuppression ± infection, bleeding (75%) (severe)</td>
<td>E</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>↑ LFTs (&lt;5%) (may be severe)</td>
<td>E</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity (21%) (severe 4%)</td>
<td>I</td>
</tr>
<tr>
<td>Injection site</td>
<td>Injection site reaction (6%)</td>
<td>I</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Musculoskeletal pain (19%)</td>
<td>E</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Leukemia (secondary) (AML, MDS)</td>
<td>D</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Cognitive disturbance (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Neuropathy (49%) (severe 4%)</td>
<td>E D</td>
</tr>
<tr>
<td></td>
<td>Seizure (rare)</td>
<td>E</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Cystoid macular edema</td>
<td>E</td>
</tr>
</tbody>
</table>
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. Febrile neutropenia occurs in 11%; this may be fatal in 1% of cases. When associated with enterocolitis, it may be life-threatening or fatal.

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.

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 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.

**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 $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/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:**

<table>
<thead>
<tr>
<th>Toxicity (worst in previous cycle)</th>
<th>Modification*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(Previous dose)</em></td>
<td>100mg/m²</td>
</tr>
<tr>
<td>Febrile neutropenia / Grade 4 ANC ≥ 7 d</td>
<td>75mg/m² (or G-CSF)</td>
</tr>
<tr>
<td>Grade 3 skin/ neuro/ major organ/ non-hematologic toxicity</td>
<td>75mg/m²</td>
</tr>
<tr>
<td>Any occurrence of cystoid macular edema</td>
<td>Hold and investigate; refer patient promptly an ophthalmic examination. Discontinue if confirmed.</td>
</tr>
<tr>
<td>Grade 4 skin/ neuro/ major organ/ non-hematologic toxicity</td>
<td>Discontinue</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Recurrence of Grade 3 toxicity after prior dose reduction</td>
<td></td>
</tr>
</tbody>
</table>

* Do not retreat until ANC ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/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.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Re-challenge</th>
</tr>
</thead>
</table>
| 1 or 2 | ● Stop or slow the infusion rate.  
 ● Manage the symptoms.  
 **Restart:** | ● Consider re-challenge with pre-medications and at a reduced infusion rate.  
 ● After 2 subsequent IRs, replace with a different taxane. Give intensified pre- |
After symptom resolution, restart with pre-medications ± reduced infusion rate. 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.

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>AST and/or ALT</th>
<th>Alkaline Phosphatase</th>
<th>Docetaxel dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; ULN AND Any</td>
<td>&gt; 1.5 x ULN</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Any AND &gt; 2.5 x ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.
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.
- To minimize exposure to DEHP leaching from PVC infusion equipment, use non-PVC (polyolefin, polypropylene) bags and administer through polyethylene lined infusion 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.
- 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.

G - Special Precautions

Contraindications:

- Patients who have a history of severe 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 10⁹/L
- Patients with severe liver impairment

Other Warnings/Precautions:

- Patients with:
  - bilirubin > ULN or
  - AST and/or ALT > 1.5 x ULN and ALP > 2.5 x ULN or
  - ANC < 1.5 x 10⁹/L
  - (refer to dose modifications section)
- Use with caution in patients with pre-existing effusions or ascites.
- Use with caution in patients who are hypersensitive to paclitaxel.
- Docetaxel contains ethanol (± 1g/m²; 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:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Mutagenicity: Yes
- Genotoxicity: Yes

Docetaxel is **contraindicated in pregnancy**. Adequate contraception must be used by both sexes, during docetaxel treatment and for at least 6 months after the last dose

- Breastfeeding: Contraindicated
- Fertility effects: Probable

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.

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)</td>
<td>↑ docetaxel exposure (up to 2.2 x) and toxicity</td>
<td>↓ metabolism of docetaxel</td>
<td>Avoid concomitant use; consider docetaxel dose ↓ if must use together (50% for strong inhibitors)</td>
</tr>
</tbody>
</table>
### Substrates or Inducers of CYP3A4 (i.e. cyclosporine, nifedipine, troleandomycin, orphenadrine, testosterone, midazolam)

<table>
<thead>
<tr>
<th>Substrates or Inducers</th>
<th>Effect on Docetaxel</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronedarone</td>
<td>↑ docetaxel severe toxicities (case report)</td>
<td>Inhibits Pgp and CYP3A4; delayed clearance of docetaxel</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>↑ systemic exposure to epirubicin or its metabolites. May be schedule dependent.</td>
<td>Docetaxel (or polysorbate 80) is suggested to interact with epirubicin metabolism and/or excretion</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>↑ docetaxel exposure</td>
<td>Unknown</td>
</tr>
<tr>
<td>CNS depressants (e.g. benzodiazepines, opioids)</td>
<td>↑ risk of CNS depression</td>
<td>Additive due to ethanol in docetaxel formulations</td>
</tr>
</tbody>
</table>

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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.

**Recommended Clinical Monitoring**

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, including nadir counts</td>
<td>Baseline and before each dose</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Baseline and before each cycle</td>
</tr>
<tr>
<td>Clinical toxicity assessment of infection, bleeding, neurotoxicity, fluid retention, hypersensitivity, lethargy, cutaneous reactions, thromboembolism, cardiovascular, musculoskeletal pain, ophthalmic, GI, respiratory effects or enterocolitis especially in the</td>
<td>At each visit</td>
</tr>
</tbody>
</table>
setting of neutropenia

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

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Docetaxel - Metastatic Castration-Resistant Prostate Cancer
- Docetaxel - Non-Small Cell Lung Cancer (NSCLC)
- Docetaxel - Non-Small Cell Lung Cancer (Second or Subsequent Line)
- Docetaxel - Neoadjuvant treatment for Non-Metastatic Breast Cancer
- Docetaxel - Metastatic Breast Cancer
- Docetaxel - Hormone Sensitive Prostate Cancer
- Docetaxel - CYCLDOCE for Early Operable Breast Cancer
- Docetaxel - FEC-D or AC-DOCE for Adjuvant Treatment for Breast Cancer

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K - References


December 2019 updated NDFP form titles

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