Docetaxel

Docetax®

Docetaxel 20 mg/0.5 mL
Docetaxel 40 mg/mL (80 mg/2mL)
Concentrate Solution for IV Infusion
Antineoplastic

FORMULATIONS
Docetaxel 20 mg / 0.5 mL Concentrate Solution for IV Infusion
Each 0.5 mL concentrate solution for intravenous infusion contains:
Anhydrous Docetaxel ..... 20 mg

Diluent (Solvent) Vial
Ethanol ..... 0.195 mL
Water for Injection q.s. ..... 1.5 mL

Docetaxel 40 mg/mL (80 mg/ 2 mL) Concentrate Solution for IV Infusion
Each mL concentrate solution for intravenous infusion contains:
Anhydrous Docetaxel ..... 40 mg

Diluent (Solvent) Vial
Ethanol ..... 0.78 mL
Water for Injection q.s. ..... 6 mL

PRODUCT DESCRIPTION
Docetaxel Concentrate Solution for IV Infusion comes in a vial and is packed with a separate solvent vial. The undiluted docetaxel concentrate solution is colorless, viscous solution, free from foreign particles intended for dilution prior to intravenous infusion. After dilution, the resulting solution is clear, colorless, very foamy and free from foreign matter.
The Diluent (Solvent) solution is a clear, colorless liquid free from foreign particles.

PHARMACOLOGY

PHARMACODYNAMICS / MECHANISM OF ACTION
Docetaxel is a taxoid antineoplastic agent. It acts by disrupting the microtubular network in cells which is essential for cell division. Docetaxel binds to free tubulin and promotes assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the formation of stable, nonfunctional microtubules which results in the inhibition of cell replication. Docetaxel's binding to the microtubules does not alter the number of protofilaments in the bound microtubules; this feature differs from other currently available taxoids.

PHARMACOKINETICS
Docetaxel exhibits dose-dependent pharmacokinetics consistent with a 3-compartment model with half-lives for the α, β and γ phases of 4 minutes, 36 minutes, and 11.1 hours, respectively. Docetaxel's initial rapid decline indicates distribution to peripheral compartments and a late (terminal) phase suggests relatively slow efflux of docetaxel from the peripheral compartment. After docetaxel IV doses of 70-115 mg/m^2 administered over 1 to 2 hours, the total body clearance averaged 21 L/hour/m^2 with an average steady-state volume of distribution of 113 L.

Docetaxel is highly bound to plasma proteins (>95%; 97% in cancer patients). Docetaxel is metabolized in the liver and undergoes oxidative metabolism of the *tert*-butyl ester group. It is not known whether docetaxel is distributed into milk. Based on *in vitro* studies, it is extensively metabolized by isoenzymes of the cytochrome P450-3A (CYP450-3A) subfamily.

Biliary excretion is the main route of elimination with approximately 75% of the administered dose excreted mainly as metabolites in the feces within 48 hours. Only 6% of docetaxel is excreted in the urine. The pharmacokinetics of docetaxel does not appear to be influenced by age or gender.

In patients with mild to moderate hepatic impairment [serum AST and/or ALT concentrations exceeding 1.5 times the upper limit of normal (ULN) and serum alkaline phosphatase concentration exceeding 2.5 times the ULN], total body clearance was lowered by an average of 27% and resulted in a 38% increase in systemic exposure (AUC) to docetaxel.

INDICATIONS
Breast Cancer
- In combination with doxorubicin and cyclophosphamide, for the adjuvant treatment of patients with operable, node-positive breast cancer.
- In combination with doxorubicin for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic chemotherapy for this condition.
- As monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Prior chemotherapy should have included an anthracycline or an alkylating agent.
- In combination with trastuzumab, for the treatment of metastatic breast cancer whose tumors overexpress HER2 and without prior chemotherapy for metastatic disease.
- In combination with capecitabine, for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

Non-Small Cell Lung Cancer (NSCLC)
- As monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy.
- In combination with cisplatin, for the treatment of patients with unresectable, locally advanced or metastatic NSCLC who have not previously received chemotherapy for this condition.

Ovarian Cancer
For the treatment of metastatic ovarian cancer after failure of first-line or subsequent therapy

Prostate Cancer
In combination with prednisone or prednisolone, for the treatment of patients with androgen independent (hormone-refractory) metastatic prostate cancer

Gastric Cancer
In combination with cisplatin and 5-fluorouracil (5-FU), for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gatroesophageal junction, who have not received prior chemotherapy for metastatic disease

Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- In combination with cisplatin and 5-FU, for the induction treatment of patients with locally advanced SCCHN.
- As monotherapy, for the treatment of patients with recurrent and/or metastatic SCCHN after failure of previous chemotherapy.

DOSAGE AND ADMINISTRATION
Patients receiving docetaxel should be under the supervision of a physician experienced in the use of chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Premedication Regimen:
- Premedicate all patients (see below for prostate cancer) with oral corticosteroids such as dexamethasone 16 mg per day (8 mg twice daily) for 5 days starting 1 day before docetaxel administration in order to reduce the incidence and severity of fluid retention and hypersensitivity reactions. (See ***Boxed Warnings, Warnings and Precautions***)

- **Premedication Regimen for Prostate Cancer Patients:** Give oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before docetaxel infusion.

General Dosing Information
Diluted docetaxel solution should be administered as a 1 hour IV infusion under ambient temperature and lighting conditions.

Spilling of the solution during docetaxel IV infusion can cause irritation, local tissue necrosis, and/or thrombophlebitis. Immediately interrupt docetaxel administration and administer the remaining dose in another vein if extravasation occurs

Recommended Docetaxel Dose (Administered as a one hour IV Infusion)
Breast Cancer
Adjuvant treatment of operable node-positive breast cancer: Docetaxel 75 mg/m^2 administered as a one-hour IV infusion given 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles. **Locally advanced or metastatic breast cancer after failure of prior chemotherapy:** • As monotherapy, docetaxel 100 mg/m^2 administered IV over 1 hour every 3 weeks. • In first-line treatment, in combination with doxorubicin 50 mg/m^2, docetaxel 75 mg/m^2, administered IV over 1 hour every 3 weeks. **In Combination with Trastuzumab for HER2 Overexpressing Breast Cancer:** Docetaxel 100 mg/m^2 every three weeks with trastuzumab administered weekly (See trastuzumab product information for dosage and administration) **In Combination with Capecitabine:** Docetaxel 75 mg/m^2 administered as a one-hour IV infusion every 3 weeks combined with capecitabine 1250 mg/m^2 twice daily (within 30 minutes after a meal) for two weeks followed by a one-week rest period. (See *capecitabine product information for dose calculation based on body surface area*).
Non-small Cell Lung Cancer (NSCLC)
Treatment after failure of prior platinum-based chemotherapy: Docetaxel 75 mg/m^2 administered IV over 1 hour every 3 weeks as a single agent. ***Treatment in patients who have not previously received chemotherapy:*** Docetaxel 75 mg/m^2 administered IV over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks.
Prostate Cancer
• Docetaxel 75 mg/m^2 administered IV over 1 hour every 3 weeks. • Administer oral prednisone or prednisolone 5 mg twice daily continuously from Day 1 and through each cycle.
Gastric Cancer
• Docetaxel 75 mg/m^2 administered IV over 1 hour followed by cisplatin 75 mg/m^2 administered as a 1 to 3 hour IV infusion (both on Day 1 only). • Starting at the end of cisplatin infusion, give 5-FU 750 mg/m^2 hour continuous infusion for 5 days. • Repeat treatment every 3 weeks. Patients should receive antiemetics and appropriate hydration for cisplatin administration. • Prophylactic G-CSF should be used to mitigate the risk of hematologic toxicities *(See **Dosage Adjustments during Treatment**)*
Head and Neck Cancer (SCCHN)
• Premedicate with antiemetics and give appropriate hydration before and after cisplatin administration. • The use of prophylactic antibiotics is recommended to reduce the incidence of neutropenia and infections. Treatment should include oral fluoroquinolones or intravenous antibiotics, for 10 days starting on day 5 of each cycle of docetaxel administration. • For dose recommendations for cisplatin and 5-FU, refer to individual product recommendations. • Prophylactic G-CSF should be used to mitigate the risk of hematologic toxicities. ***Induction Chemotherapy Followed by Radiotherapy:*** • Docetaxel 75 mg/m^2 administered IV over 1 hour followed by cisplatin 75 mg/m^2 IV over 1 hour (Day 1) followed by 5-FU 750 mg/m^2 per day as a continuous IV infusion for 5 days (Days 1-5) initiated after cisplatin infusion. This regimen is administered every 3 weeks for 4 cycles. • Patients should receive radiotherapy after completion of chemotherapy. ***Induction Chemotherapy Followed by Chemoradiotherapy:*** • Docetaxel 75 mg/m^2 administered IV over 1 hour (Day 1), followed by cisplatin 100 mg/m^2 as a 30 minute to 3 hour IV infusion (Day 1), followed by 5-FU 1000 mg/m^2 per day as a continuous IV infusion for 4 days (Days 1 to 4). This regimen is administered every 3 weeks for 3 cycles. • Patients should receive chemoradiotherapy after chemotherapy.
Or, as prescribed by a physician.

Dosage Adjustments During Treatment
General
- Administer docetaxel therapy when neutrophil count is ≥ 1,500 cells/mm^3.
- Reduce docetaxel dose from 100 mg/m^2 to 75 mg/m^2 and/or 75 mg/m^2 to 60 mg/m^2 in patients who develop either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy.
- If the patient continues to experience these reactions at 60 mg/m^2, docetaxel therapy should be discontinued.

Adjuvant Therapy for Breast Cancer
- Administer G-CSF to provide prophylactic coverage (e.g., day 4 to 11) in all subsequent cycles of docetaxel in breast cancer patients who develop complicated neutropenia (including prolonged neutropenia, febrile neutropenia or infection). If these symptoms continue to occur, patients should remain on G-CSF and reduce their docetaxel dose to 60 mg/m^2.
- Neutropenia could occur earlier; hence, G-CSF use should be based on the neutropenic risk of the patient and current recommendations. Docetaxel dose should be decreased to 60 mg/m^2 in patients who experience Grade 3 or 4 stomatitis.

In Combination with Cisplatin
Docetaxel should be reduced from 75 to 65 mg/m^2 for:
- Patients with platelet count nadir of < 25,000 cells/mm^3 during the previous course of therapy, **OR**
- Patients who experience febrile neutropenia, **OR**
- Patients with serious non-hematologic toxicities

For cisplatin dosage adjustments, see cisplatin product information.

In Combination with Capecitabine
- For patients developing the first appearance of a Grade 2 toxicity, which persists at the time of the next docetaxel/capecitabine treatment, delay treatment until resolved to Grade 0 to 1 then resume original dose.
- For patients developing the second appearance of a Grade 2 or first appearance of a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0 to 1 then resume with 55 mg/m^2 docetaxel treatment
- Discontinue docetaxel for any subsequent appearances of toxicities or any Grade 4 toxicities.
  For capecitabine dosage adjustments, see capecitabine product information.

In Combination with Cisplatin and 5-FU
- If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite the C-GSF use, docetaxel dose should be reduced from 75 to 60 mg/m^2.
- If subsequent episodes of complicated neutropenia still occur, docetaxel dose should be reduced from 60 to 45 mg/m^2.
- In case of Grade 4 thrombocytopenia, docetaxel dose should be reduced from 75 to 60 mg/m^2.
- Do not administer subsequent cycles of docetaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.
- See table below for dosage adjustments for gastrointestinal (GI) toxicities.
- Discontinue docetaxel treatment if toxicities persist.

Recommended Dose Adjustments for GI Toxicities in Patients Treated with Docetaxelin Combination with Cisplatin and 5-FU	
Toxicity	***Dosage Adjustment***
Diarrhea (Grade 3)	1st Episode: Reduce 5-FU dose by 20% 2nd Episode: Then reduce docetaxel dose by 20%.
Diarrhea (Grade 4)	1st Episode: Reduce docetaxel and 5-FU doses by 20%. 2nd Episode: Discontinue treatement.
Stomatitis / Mucositis (Grade 3)	1st Episode: Reduce FU dose by 20%. 2nd Episode: Stop 5-FU only, at all subsequent cycles 3rd Episode: Reduce docetaxel dose by 20%.
Stomatitis / Mucositis (Grade 4)	1st Episode: Discontinue 5-FU only, at all subsequent cycles 2nd Episode: Reduce docetaxel dose by 20%.

For cisplatin and 5-FU dosage adjustments, see individual product information.

Special Populations
Patients with Hepatic Impairment: Adjust doses based on levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) as indicated in the table below:

ALT and/or AST Levels	AP Levels	Bilirubin	Recommended Dose
Patients treated with 100 mg/m^2			
> 1.5 x ULN	> 2.5 x ULN	---	75 mg/m^2
> 3.5 x ULN	> 6 x ULN	> ULN	NOT RECOMMENDED UNLESS STRICTLY INDICATED
Patients treated with 75 mg/m^2			
> 3.5 x ULN	> 6 x ULN	> ULN	NOT RECOMMENDED UNLESS STRICTLY INDICATED
Patients treated with docetaxel, cisplatin and 5-FU for gastric adenocarcinoma			
> 1.5 x ULN	> 2.5 x ULN	> 1 x ULN	NOT RECOMMENDED UNLESS STRICTLY INDICATED

Use in Children: Limited clinical data is available to establish safety and effectiveness of docetaxel in children.
Use in the Elderly: No special dose adjustment is recommended. In combination with capecitabine, capecitabine dose should be reduced *(see capecitabine product information)*

Preparation of Dosage Form:
Docetaxel Concentrate Solution for IV infusion requires **two** dilutions prior to IV infusion.

A. Preparation of Initial Diluted Solution
1. From the refrigerator, get appropriate number of vials of docetaxel concentrate solution and accompanying diluent and allow the vials to stand at room temperature for approximately 5 minutes.
2. Withdraw contents from the appropriate diluent vial into a syringe using aseptic technique. Transfer it to an appropriate vial of docetaxel concentrate solution. An initial diluted 10 mg/mL docetaxel solution will result if the procedure is followed as described. Both the docetaxel and diluent solutions are overfilled to guarantee a final premix solution concentration of 10 mg/mL.
3. Gently rotate the diluted solution (for approximately 15 seconds) to assure full mixture of concentrate and diluent.
4. Initial diluted docetaxel solution (10 mg/mL) should be clear. However, foam may be formed on top of the solution due to polysorbate 80. This foam dissipates after standing the solution for a few minutes. It is not required that all foam dissipate before continuing the preparation process.

B.Preparation of Final Dilution for Infusion
1. Using a calibrated syringe, aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg/mL) and inject into a 250 mL infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.9 mg/mL. Use a larger volume of the infusion vehicle if a dose greater than 240 mg of docetaxel is needed. A docetaxel concentration of 0.9 mg/mL should not be exceeded.
2. Manually rotate the infusion to thoroughly mix the solution.
3. Visually inspect the solution for particulate matter or discoloration prior to use. Discard if docetaxel for injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation.

STABILITY AFTER RECONSTITUTION
The product is stable up to 8 hours after reconstitution with a vial of diluent when stored under refrigeration (2°C - 8°C). After further dilution with 5% dextrose solution or 0.9% sodium chloride, the product is stable up to 4 hours when stored between 15°C - 30°C.

Handling and Disposal Precautions
- The use of protective gloves is highly recommended in handling docetaxel.
- Wash the affected area immediately and thoroughly with soap and water if docetaxel comes in contact with skin. If solution comes in contact with mucous membrane, immediately wash affected area with water.
- Undiluted docetaxel should **NOT** come in contact with plasticized polyvinyl chloride (PVC) equipment or devices. Docetaxel should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-covered administration sets to avoid leaching from PVC infusion bags or sets.

CONTRAINDICATIONS
- Hypersensitivity to docetaxel, polysorbate 80, or any component of the product.
- Baseline neutrophil count < 1500 cells/mm^3
- Patients under Disulfiram treatment
- Severe liver impairment
- Pregnant or breastfeeding women

Contraindications for other drugs (e.g., doxorubicin, cyclophosphamide, trastuzumab, capecitabine, cisplatin, prednisone, and 5-FU) also apply when such drugs are combined with docetaxel.

WARNINGS and PRECAUTIONS
- Docetaxel should be administered under the supervision of a physician experienced in the use of antineoplastic agents.
- The incidence of treatment-related mortality associated with docetaxel is increased in patients with abnormal liver function and in patients receiving docetaxel at 100 mg/m^2.
- Docetaxel should generally not be given to patients with bilirubin > ULN, or to patients with AST and/or ALT > 1.5 x ULN concomitant with AP > 2.5x ULN. Liver function test elevations increase the risk of severe or life-threatening complications. Obtain liver function test before each cycle.
- Docetaxel should not be given to patients with neutrophil counts of <1500 cells/mm^3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed in all patients receiving docetaxel.
- Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in 0.9% of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. (see ***Warnings and Precautions***) Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. *(See **Contraindications**)*
- Severe fluid retention may occur despite dexamethasone *(see **Warnings and Precautions**)*
- Treatment-related acute myeloid leukemia may occur *(see **Warnings and Precautions**)*

General
All patients should be premedicated with an oral corticosteroid such as dexamethasone prior to docetaxel administration (see ***Dosage and Administration***)

Toxic Deaths
Docetaxel has been associated with deaths considered possibly or probably related to treatment in patients with metastatic breast cancer. These were patients who are previously treated or untreated, with normal baseline liver function and those with various tumor types who had abnormal baseline liver function. Almost half of the accounted deaths occurred during the first cycle with sepsis as the major cause.
Deaths were also reported in patients with locally advanced or metastatic NSCLC who had a history of prior platinum-based chemotherapy. (see ***Boxed Warnings***)

Acute Myeloid Leukemia
In clinical trials, treatment-related myeloid leukemia (AML) or myelodysplasia have occurred in patients receiving docetaxel, doxorubicin and cyclophosphamide. These patients required hematological follow-up.

Fluid Retention
Severe fluid retention has been reported. Incidence and severity of fluid retention is cumulative and slowly reversible after discontinuation of docetaxel therapy and may be reduced by oral corticosteroids. Patients with severe fluid retention (e.g., pleural effusion, pericardial effusion and ascites) should be monitored more closely for the possible exacerbation of the effusions.

Hematologic Effects (see Boxed Warnings)
Docetaxel may cause bone marrow suppression and other hematologic effects such as neutropenia. To monitor for the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients taking docetaxel. The median day to nadir was 7 days but this interval may be shorter in heavily pretreated patients.

Hepatic Impairment (see Boxed Warnings and Use in High Risk Groups)

Hypersensitivity Reactions (see Boxed Warnings)
Closely observe hypersensitivity reactions especially during the first and second infusions. Since hypersensitivity reactions (e.g., flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, and drug fever or chills) may occur within a few minutes, during or immediately after the cessation of docetaxel infusion, facilities for the treatment of hypotension and bronchospasm should be readily available. If minor reactions (e.g., flushing or localized skin reactions) occur, interruption of therapy is not required. Patients who experience severe hypersensitivity reactions should immediately discontinue the use of docetaxel and should not be rechallenged with the drug.

Neurologic Effects
Dose reduction may be required in patients who develop severe neurosensory signs and/or symptoms such as paresthesia, dysesthesia and pain. Treatment should be discontinued if patients continue to experience these symptoms. *(see **Dosage and Administration**)*

Cutaneous Reactions
Mild to moderate reversible cutaneous reactions characterized by rash including localized eruptions mainly on feet, hands (including hand and foot syndrome), but also arms, face or thorax, and frequently associated with pruritus may occur within one week after docetaxel infusion. Eruptions generally occurred within one week after docetaxel infusion, recovered before the next infusion and were not disabling. Severe symptoms such as eruptions followed by desquamation which rarely lead to discontinuation of docetaxel have been less frequently reported. Nail disorders were distinguished by hypo- or hyperpigmentation, pain, and onycholysis.

Asthenia
Severe asthenia has occurred in breast cancer patients. Symptoms of fatigue and weakness which may be associated with deterioration of performance status in patients with progressive disease may last for a few days up to several weeks.

Carcinogenicity, Mutagenicity, Impairment of Fertility
No studies have been conducted to fully assess docetaxel's long-term carcinogenic potential. However, based on its pharmacodynamic mechanism of action, docetaxel may be a carcinogen.

Docetaxel has been shown to be mutagenic in the *in vitro* chromosome aberration test in CHO-K, cells and in the *in vivo* micronucleus test in the mouse, but did not induce mutagenicity in the Ames test or the CHO/HPRT gene mutation assays.

Docetaxel can be genotoxic. Men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to docetaxel therapy.

INTERACTIONS WITH OTHER MEDICAMENTS
Docetaxel's metabolism may be altered *in vitro* by concomitant administration of compounds that induce, inhibit or are metabolized by CYP450 3A4. Docetaxel's biotransformation was inhibited by ciclosporin, terfenadine, ketoconazole, erythromycin, and troleandomycin and to a lesser extent by doxorubicin, vinorelbine, vinblastine, and nifedipine; increased by dexamethasone, phenobarbital and clofibrate; and unaffected by cimetidine, ranitidine, omeprazole, diazepam, imipramine, paracetamol, caffeine, tolbutamide, and quinidine. Exercise caution with these drugs when treating patients receiving docetaxel.

Although prednisolone is known to inhibit CYP450 3A4, no statistically significant effect of prednisolone on the pharmacokinetics of docetaxel was observed.

Docetaxel is highly protein-bound (> 95%). The *in vitro* plasma protein binding of docetaxel was not affected by dexamethasone, erythromycin, salicylate, sulfamethoxazole, diphenhydramine, propranolol, profenone, phenytoin, and sodium valproate. The binding of digoxin was not affected by docetaxel. Dexamethasone did not affect protein binding of docetaxel.

Antineoplastics
- The clearance of docetaxel was reduced when administered after 4 days of topotecan treatment (rather than on day 1); this worsened neutropenia.
- Concomitant administration with doxorubicin resulted in an increased incidence of febrile neutropenia.
- Moderate to severe heart failure, occasionally fatal, have been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline therapy (e.g., doxorubicin and epirubicin). Patients for treatement with the combination of docetaxel and trastuzumab should undergo baseline cardiac assessment. Cardiac function should be further monitored during treatment to identify the development of cardiac dysfunction.
- Co-administration of docetaxel with carboplatin resulted in about 50% higher carboplatin clearance compared with carboplatin monotherapy.
- No pharmacokinetic interaction was seen with the combination of docetaxel, doxorubicin and cyclophosphamide.

HIGH RISK GROUPS
Use in Pregnancy and Breastfeeding
Pregnancy: Pregnancy Category D
Docetaxel can cause fetal harm when administered to pregnant women and therefore must not be used during pregnancy. Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform their physician immediately should pregnancy occur. Patients should be informed of the potential hazards of the drug to the baby. Contraceptive measures must be taken during and at least three months after cessation of therapy with docetaxel.

Studies in rats and rabbits have shown docetaxel to be embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay) at doses ≥ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis. These doses have also caused maternal toxicity.

Breastfeeding: Docetaxel is lipophilic but it is not known whether it is distributed into human milk. Breastfeeding is not recommended during chemotherapy because of the potential serious adverse reactions to docetaxel by the breastfeeding infant.

Use in the Elderly
Based on population pharmacokinetics, no dosage adjustment is required in these patients. However, analysis of safety data in elderly patients (≥ 60 years old) receiving docetaxel in combination with capecitabine has shown an increased incidence of treatment-related Grade 3 or 4 adverse reactions, treatment-related serious adverse reactions and early withdrawals from treatment due to adverse reactions compared with patients < 60 years old.

Use in Children
The safety and efficacy of docetaxel in children < 16 years old have not been established.

Use in Patients with Liver Impairment
Measure liver function tests at baseline and before each cycle of docetaxel administration. *(see **Boxed Warnings, Warnings and Precautions**)*

Use in Patients with Renal Impairment
No dosage adjustment is required in patients with renal impairment. A 75% dose reduction of capecitabine is recommended when used in combination with docetaxel in patients with moderate renal impairment.

UNDESIRABLE EFFECTS
Hematologic Effects: Reversible and non-cumulative neutropenia is the most frequent adverse event seen with docetaxel; severe anemia, myelosuppression (dose-limiting adverse effect), febrile neutropenia, and leukopenia; bleeding and gastrointestinal hemorrhage associated with severe thrombocytopenia *(see **Warnings and Precautions**)*.
Gastrointestinal (GI) Effects: Mild to moderate nausea, vomiting, and diarrhea; anorexia and taste perversion. Docetaxel-induced stomatitis (mucositis) characterized by diffuse ulceration of the lips, tongue and oral cavity may be experienced especially in patients with increased liver enzymes. Other adverse effects may include constipation, duodenal ulcer, esophagitis, intestinal obstruction, ileus, dehydration associated with GI disorders, anorexia, ischemic colitis and abdominal pain. Rarely, fatal GI hemorrhage associated with severe neutropenia, mucositis, and neutropenic enterocolitis have also been reported. A case report of typhitis (neutropenic enterocolitis) and fatal sepsis secondary to *Clostridium septicum* has also been reported in patients taking docetaxel.
Cardiovascular Effects: Hypotension; rare cases of heart failure, thromboembolism, myocardial infarction, sinus tachycardia, atrial flutter, dysrrhythmia, unstable angina, and hypertension.
Hypersensitivity Reactions: Flushing, skin rashes with or without pruritus, chest tightness, back pain, drug-associated fever or chills; severe reactions characterized by hypotension, bronchospasm, skin rash or generalized erythema were observed after initiating docetaxel infusion.
Fluid retention: Fluid retention (with or without premedication), including edema and less frequently, pleural effusion, ascites, pericardial effusion, and weight increase; fluid retention beginning in the lower limbs, but became generalized, with a weight increase of 3 kg or more *(see **Boxed Warnings, Warnings and Precautions**).*
Fluid retention was not associated with acute episodes of dehydration, oliguria or hypotension, and slowly abated after discontinuation of therapy.
Dermatologic Effects: Alopecia has a sudden onset and occurs 14 to 21 days after administration of docetaxel. Alopecia is dose-related and generally occurs at doses exceeding 55 mg/m^2. Skin rash (occasionally associated with pruritus), including localized rashes, especially in the hands and feet, but they were also seen in the arms face and thorax; severe nail disorders, including hypopigmentation or hyperpigmentation, occasional onycholysis and pain may occur.
Other skin disturbances include cutaneous lupus erythematosus and bullous eruptions, radiation recall reactions, and rarely Stevens Johnson Syndrome and toxic epidermal necrolysis.
Nervous System Effects: Neurosensitivity symptoms, such as paresthesia, dysesthesia with numbness and tingling in a stocking-and-glove distribution; pain (including burning); proximal and distal muscle weakness, dizziness, confusion, seizure, and loss of consciousness.
Infusion Site Reactions: Mild infusion site reactions include hyperpigmentation, inflammation, local erythema, skin dryness, redness, or phlebitis. Thrombophlebitis or extravasation and swelling of the vein were also observed.
Hepatic Effects: Increased AST, ALT and AP up to levels that exceeded 2.5 times the ULN; jaundice (especially when used in combination with capecitabine). There were also observed bilirubin values > 2.5 of the ULN. *(See **Boxed Warnings, Warnings and Precautions**)*
Musculoskeletal: Asthenia, myalgia, arthralgia, and fatigue.
Respiratory Effects: Bronchospasm associated with hypersensitivity, pleural effusion or dyspnea as manifestations of fluid retention, acute pulmonary edema, acute respiratory distress syndrome, and interstitial pneumonia.
Ophthalmic Effects: Excessive tear formation (epiphora) and canalicular stenosis that were reported to be more severe in patients who receive docetaxel weekly than those receiving docetaxel every 3 weeks. Visual disturbances (e.g., flashing, scotomata) very rarely occurred during docetaxel infusion. Ophthalmic effects from docetaxel are reversible.
Otic Effects: Ototoxicity, hearing disorders and/or hearing loss have been reported in patients receiving docetaxel, including some cases associated with other ototoxic agents.
Other Effects: Infection, fever, tumor lysis syndrome, diffused pain, chest pain, and renal insufficiency.

OVERDOSE AND TREATMENT
There is limited clinical experience on docetaxel overdose. Since there is no known antidote for docetaxel intoxication, patients must be admitted to a specialized unit where vital signs could be monitored. Anticipated complications may include bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should be given G-CSF as soon as overdose is discovered. Other supportive therapy may be administered as needed.

Two cases of docetaxel overdose have been reported. Patients, who both recovered, were reported to experience severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia after a 1 hour IV infusion of 150-200 mg/m^2 docetaxel.

STORAGE CONDITIONS
Store at temperatures between 2°C - 8°C. Protect from light.

AVAILABILITY
Docetax 20mg/0.5mL Concentrate Solution for IV Infusion - Box of 1 (Type I glass vial) with 1.5 mL Diluent Vial (Type I glass vial)
Docetax 40mg/mL (80 mg\2 mL)Concentrate Solution for IV Infusion - Box of 1 (Type I glass vial) with 6.0 mL Diluent Vial (Type I glass vial)

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by Laboratorios Richmond S.A.C.I.F.
Elcano 4938, Ciudad Autonoma
de Buenos Aires, Republica Argentina
Imported and Distributed by
United Laboratories, Inc.
66 United Street, Mandaluyong City, Philippines
for BIOMEDIS, INC.
Dynavision Bldg.,108 Rada St., Legaspi Village, Makati City, Philippines

Date of Revision: September 2011