low as 1/50 and 1/300 the recommended human dose on a body surface area basis.
There are no adequate and well-controlled studies in pregnant women using Docetaxel. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.
In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel, close monitoring for toxicity and a Docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor can not be avoided.

ADVERSE REACTIONS

The most serious adverse reactions from Docetaxel are:
- Toxic Deaths
- Hepatotoxicity
- Neutropenia
- Hypersensitivity
- Fluid Retention
- Acute Myeloid Leukemia
- Neurologic Reaction
- Asthenia

(See warning and precaution for more information)

The most common adverse reactions across all Docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.
Body as a whole: diffuse pain, chest pain, radiation recall phenomenon.
Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction.
Cutaneous: very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Scleroderma-like changes usually preceded by peripheral lymphedema. In some cases multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported.
Gastrointestinal: abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, ischemic colitis, colitis, intestinal obstruction, ileus, neutropenic enterocolitis and dehydration as a consequence to gastrointestinal events have been reported.
Hematologic: bleeding episodes. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported. Cases of acute myeloid leukemia and myelodysplasic syndrome have been reported in association with Docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.
Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication.
Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.
Neurologic: confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.
Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.
Hearing: rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.
Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome, interstitial pneumonia. Pulmonary fibrosis has been rarely reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.
Renal: renal insufficiency and renal failure have been reported, the majority of these cases were associated with concomitant nephrotoxic drugs.
Metabolism and Nutrition disorder: cases of hyponatremia have been reported.

OVERDOSAGE

There is no known antidote for Docetaxel overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.
In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.
In mice, lethality was observed following single intravenous doses that were $\geq$ 154 mg/kg (about 4.5 times the human dose of 100 mg/m^2 on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5 times the human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

CLINICAL PHARMACOLOGY

Mechanism of Action:
Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

Pharmacokinetics
Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1 -acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.
Metabolism: In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Elimination: A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Effect of Age: A population pharmacokinetic analysis was carried out after Docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with Docetaxel. Patients with severe hepatic impairment have not been studied.

INCOMPATIBILITIES

Contact of the Docetaxel with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

STORAGE

Store at a temperature not exceeding 25°C. Protect from light.
Stability: Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration).
Also, physical and chemical in use stability of the infusion solution prepared as recommended has been demonstrated in non PVC bags upto 48 hours when stored at 2°C and 8°C (36°F and 46°F).

Docetaxel infusion solution is supersaturated, therefore may crystallize over time. if crystals appear, the solution must no longer be used and shall be discarded.

HANDLING AND DISPOSAL

Handling
As with other antineoplastic agents, Docetaxel must be prepared and handled with caution Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel solutions. The use of gloves is recommended.
If Docetaxel Injection, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.
Disposal:
All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents. Any unused product or waste material should be disposed of in accordance with local requirements.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The alcohol content in docetaxel injection may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Docetaxel Injection on the ability to drive and use machine immediately after the infusion. Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of docetaxel injection and advised not to drive or operate machinery if these symptoms occur.

PRESENTATION / PACKAGING

Docetaxel Injection is presented in 3 strengths as 20mg/ml, 80mg/4ml and 120mg/6ml as a sterile, single use vial. Taxewell-RTU is one vial formulation. Ready to add to Infusion solution without prior dilution with a solvent.

References:

- Pack Insert of Docetaxelof Sanofi Aventis.
- Brunton, L. L.; Chabner, Bruce; Knollmann, Bjorn C., eds. (2011). Goodman and Gilman's The Pharmacological Basis of Therapeutics (12th ed.). New York: McGraw-Hill.
- http://www.medicines.org.uk/emc/medicine/25464/SPC

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GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Docetaxel Injection IP

Taxewell-RTU™

टेक्सीवेल आर. टी. यू.

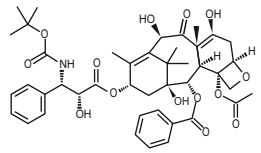
Ready to add to Infusion solution
For IV Infusion only
Rx only

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

- The incidence of treatment-related mortality associated with Docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive Docetaxel as a single agent at a dose of 100 mg/m^2.
- Docetaxel should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel therapy.
- Docetaxel therapy 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 on 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 patients who received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and administration of appropriate therapy. 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.
- Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}\,3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

Docetaxel Injection is a sterile, non-pyrogenic, clear and colorless to slight yellowish solution. Each ml contains 20 mg docetaxel (anhydrous). Docetaxel is a sterile solution, available in 20mg/ml 80mg/4ml and 120mg/6ml single dose vials where each ml contains Docetaxel (anhydrous) 20mg.
Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution.

COMPOSITION

Docetaxel Injection IP 20mg/ml, 80mg/4ml and 120mg/6ml

Each ml contains	
Docetaxel Trihydrate IP eq. to	
Anhydrous Docetaxel IP	20mg
Citric Acid IP	4mg
Polysorbate 80 IP	520mg
Ethanol IP	395mg

INDICATIONS

Breast Cancer
Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node positive breast cancer.
Non Small Cell Lung Cancer
Docetaxel as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum based chemotherapy.
Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non small cell lung cancer who have not previously received chemotherapy for this condition.
Prostate Cancer
Docetaxel in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.
Gastric Adenocarcinoma
Docetaxel in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

Head and Neck Cancer
Docetaxel in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN)

DOSAGE AND ADMINISTRATION

Docetaxel is strictly recommended to be used as I.V. infusion only.
Recommended Dose
Breast Cancer
•The recommended dose of Docetaxel is 60-100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
•In the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.
Non Small Cell Lung Cancer (NSCLC)
•For treatment after failure of prior platinum based chemotherapy, evaluation of Docetaxel as monotherapy, the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment related mortality in randomized, controlled trials.
•For chemotherapy naive patients, Docetaxel evaluation in combination with cisplatin has resulted in the recommended dose of 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks.
Prostate cancer
•For hormone refractory metastatic prostate cancer, the recommended dose of Docetaxel is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion along with continuous administration of prednisone 5 mg (oral) twice daily.
Gastric adenocarcinoma
•For gastric adenocarcinoma, the recommended dose of Docetaxel is 75 mg/m^2 as 1 hour intravenous infusion, followed by cisplatin 75 mg/m^2, as 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as 24 hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks.
Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration.
Head and Neck cancer
Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered.
All patients treated on the Docetaxel containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.
Induction chemotherapy followed by radiotherapy (TAX323)
For the induction treatment of locally advanced inoperable SCCHN, the
recommended dose of Docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.
Induction chemotherapy followed by chemoradiotherapy (TAX324)
For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of Docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy
Premedication Regimen
•All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to Docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.
•For hormone refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours and 1 hour before the Docetaxel infusion.

Dosage adjustments during treatment
Breast Cancer
Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during Docetaxel therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during Docetaxel therapy may tolerate higher doses. Patients who develop ≥ grade 3 peripheral neuropathy should have Docetaxel treatment discontinued entirely.
Combination Therapy with Docetaxel in the Adjuvant Treatment of Breast Cancer: Docetaxel in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have the Docetaxel dose reduced to 60 mg/m^2. Patients who experience Grade 3 or 4 stomatitis should have the Docetaxel dose decreased to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel therapy should have the dosage of Docetaxel reduced from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non Small Cell Lung Cancer
Monotherapy with Docetaxel for NSCLC treatment after failure of prior platinum-based chemotherapy: Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during Docetaxel treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ grade 3 peripheral neuropathy should have Docetaxel treatment discontinued entirely.
Combination therapy with Docetaxel for chemotherapy naive NSCLC: Patients who are dosed initially at Docetaxel 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the Docetaxel dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended.

Prostate Cancer
Combination therapy with Docetaxel for hormone-refractory metastatic prostate cancer: Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel therapy should have the dosage of Docetaxel reduced from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Gastric or Head and Neck Cancer
Docetaxel in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer Patients treated with Docetaxel in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the Docetaxel dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the Docetaxel dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the Docetaxel dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category D.
Based on its mechanism of action and findings in animals, Docetaxel can cause fetal harm when administered to a pregnant woman. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.
Docetaxel can cause fetal harm when administered to a pregnant woman. Studies in both rats and rabbits 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, have shown that Docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.
Nursing Mothers
It is not known whether docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Docetaxel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
The efficacy of Docetaxel in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of Docetaxel in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.
Docetaxel has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluorouracil (TCF).
Docetaxel Monotherapy **:** Docetaxel monotherapy was evaluated in a dose-finding phase 1 trial in 61 pediatric patients (median age 12.5 years, range 1-22 years) with a variety of refractory solid tumors. The recommended dose was 125 mg/m^2 as a 1-hour intravenous infusion every 21 days. The primary dose limiting toxicity was neutropenia.
The recommended dose for Docetaxel monotherapy was evaluated in a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1-26 years) with a variety of recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.
Docetaxel in Combination **:** Docetaxel was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma (NPC) in pediatric patients prior to chemoradiation consolidation. Seventy-five patients (median age 16 years, range 9 to 21 years) were randomized (2:1) to Docetaxel (75 mg/m²) in combination with cisplatin (75 mg/m²) and 5-fluorouracil (750 mg/m²) (TCF) or to cisplatin (80 mg/m²) and 5-fluorouracil (1000 mg/m²/day) (CF). The primary endpoint was the CR rate following induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response.

Geriatric Use
In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients

Hepatic Impairment
Patients with bilirubin >ULN should not receive Docetaxel. Also, patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN should not receive Docetaxel.

Administration
Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel solutions. The use of gloves is recommended.
If Docetaxel Injection, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

Incompatibilities: Contact of the Docetaxel with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Dilution Guidelines:
One Vial Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution
• Docetaxel vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection vials to stand at room temperature for approximately 5 minutes before use
• Aseptically withdraw the required amount of Docetaxel injection (20 mg docetaxel/mL) with a calibrated syringe 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 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of Docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel is not exceeded
• Thoroughly mix the infusion by gentle manual rotation.
• As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.
• The Docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature (below 25°C) and lighting conditions

Stability
Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1 hour intravenous administration).
Also, physical and chemical in use stability of the infusion solution prepared as recommended has been demonstrated in non PVC bags upto 48 hours when stored at 2°C and 8°C (36°F and 46°F) .

Docetaxel infusion solution is supersaturated, therefore may crystallize over time. if crystals appear, the solution must no longer be used and shall be discarded.

CONTRAINDICATION:

• Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred
• Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm^3.
• Pregnant women
• During Breast Feeding
• Patients with severe liver impairment

WARNING AND PRECAUTIONS:

Toxic Deaths
Breast Cancer
Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.
Non-Small Cell Lung Cancer
Docetaxel administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry.

Hepatic Impairment
Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel.

Hematologic Effects
Perform frequent peripheral blood cell counts on all patients receiving Docetaxel. Patients should not be retreated with 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. A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel cycle.

Hypersensitivity Reactions
Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel.
Hypersensitivity reactions may occur within a few minutes following initiation of a Docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of Docetaxel.

Fluid Retention
Severe fluid retention has been reported following Docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel administration to reduce the incidence and severity of fluid retention.

Acute Myeloid Leukemia
Treatment-related acute myeloid leukemia (AML) or myelodysplasia has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. In the adjuvant breast cancer trial (TAX316) AML occurred in 3 of 744 patients who received Docetaxel, doxorubicin and cyclophosphamide (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide In TAC treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires haematological follow-up.

Cutaneous Reactions
Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued Docetaxel due to skin toxicity.

Neurologic Reactions
Severe neurosensory symptoms (e.g. paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued.

Asthenia
Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Alcohol Content
Cases of intoxication have been reported with some formulation of Docetaxel due to the alcohol content. The alcohol content in a dose of docetaxel injection may affect the central nervous system and should be taken into account for patient in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in Docetaxel Injection on the ability to drive or use machines immediately after the infusion.

Use in Pregnancy
Docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as