Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis have rarely been reported and may be associated with fatal outcome. 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 disorders: electrolyte imbalance, including cases of hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia has been reported.

7 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 INJECTION and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with DOCETAXEL INJECTION, close monitoring for toxicity and a DOCETAXEL INJECTION dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action, DOCETAXEL INJECTION can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Limited available human data are not sufficient to inform the drug-associated risk during pregnancy. In animal reproduction studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused an increased incidence of embryo-fetal toxicities, including intra-uterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively *(see Data)*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Intravenous administration of ≥ 0.3 and 0.03 mg/kg/day docetaxel to pregnant rats and rabbits, respectively, during the period of organogenesis caused an increased incidence of intrauterine mortality, resorptions, reduced fetal weights and fetal ossification delays. Maternal toxicity was also observed at these doses, which were approximately 0.02 and 0.003 times the daily maximum recommended human dose based on body surface area, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of docetaxel in human milk, or on its effects on milk production or the breast-fed child. No lactation studies in animals have been conducted. Because of the potential for serious adverse reactions in a breast-fed child from docetaxel exposure, including toxic death, hepatotoxicity, neutropenia, and acute myeloid leukemia, advise women not to breastfeed during treatment with DOCETAXEL INJECTION and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating DOCETAXEL INJECTION.

Contraception

Females

DOCETAXEL INJECTION can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of DOCETAXEL INJECTION.

Males

Based on genetic toxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months following the last dose of DOCETAXEL INJECTION *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on findings in animal studies, DOCETAXEL INJECTION may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The alcohol content of DOCETAXEL INJECTION should be taken into account when given to pediatric patients *[see Warnings and Precautions (5.12)]*.

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.

Another formulation of 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-fluoruracil (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/m^2) in combination with cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2) (TCF) or to cisplatin (80 mg/m^2) and 5-fluorouracil (1,000 mg/m^2/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.

Pharmacokinetics
Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2.

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.2±2.57 μg.h/mL.

In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults *[see Clinical Pharmacology (12.3)]*.

8.5 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.

Non-Small Cell Lung Cancer
In a study conducted in chemotherapy-naive patients with NSCLC (TAX326), 148 patients (36%) in the docetaxel+cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the docetaxel+cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI: 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI: 9.3 months, 14 months). In patients 65 years of age or greater treated with docetaxel+cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with docetaxel+cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When docetaxel was combined with carboplatin for the treatment of chemotherapy-naive, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared

to similar patients treated with docetaxel+cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Prostate Cancer
Of the 333 patients treated with docetaxel every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the following treatment emergent adverse reactions occurred at rates ≥10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs. 59%), infection (37% vs. 24%), nail changes (34% vs. 23%), anorexia (21% vs. 10%), weight loss (15% vs. 5%) respectively.

Breast Cancer
In the adjuvant breast cancer trial (TAX316), docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Gastric Cancer
Among the 221 patients treated with docetaxel in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ≥10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Head and Neck Cancer
Among the 174 and 251 patients who received the induction treatment with docetaxel in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.

These clinical studies of docetaxel in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

Patients with bilirubin > ULN should not receive DOCETAXEL INJECTION. Also, patients with AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN should not receive DOCETAXEL INJECTION *[see Boxed Warning, Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.

The alcohol content of DOCETAXEL INJECTION should be taken into account when given to patients with hepatic impairment *[see Warnings and Precautions (5.12)]*.

10 OVERDOSAGE

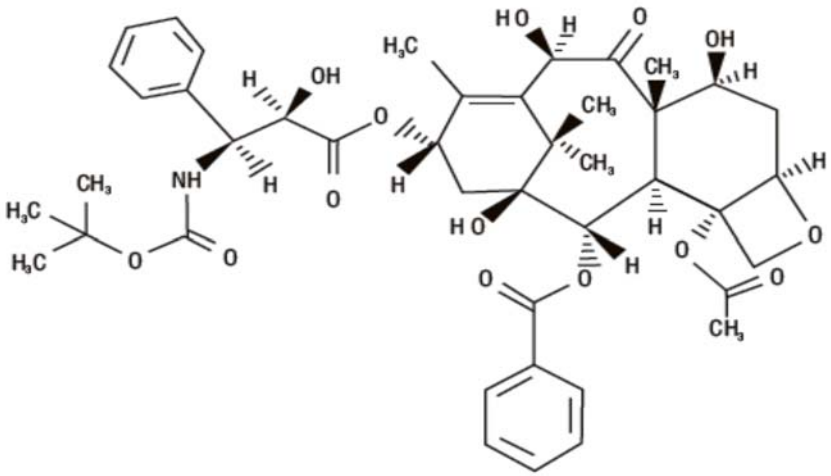
There is no known antidote for DOCETAXEL INJECTION overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients 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 ≥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.

11 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 (anhydrous) 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. Docetaxel (anhydrous) has the following structural formula:



Docetaxel anhydrous, USP is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$, and a molecular weight of 807.88. It is highly lipophilic and practically insoluble in water.

<u>One-vial DOCETAXEL INJECTION</u>

DOCETAXEL INJECTION USP requires NO prior dilution with a diluent and is ready to add to the infusion solution.

DOCETAXEL INJECTION USP is a sterile, non-pyrogenic, yellowish colour solution at 20 mg/mL concentration.

Each mL contains 20 mg docetaxel (anhydrous) 4 mg citric acid anhydrous in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution.

DOCETAXEL INJECTION USP is available in single-dose vials containing 20 mg (1 mL), 80 mg (4 mL), or 160 mg (8 mL) docetaxel (anhydrous).

12 CLINICAL PHARMACOLOGY

12.1 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.

12.3 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 *[see Drug Interactions (7)]*.

Elimination

A study of ^{14}C-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.

Specific Populations

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 *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Drug Interaction Studies

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m^2 intravenous) alone or docetaxel (10 mg/m^2 intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was coadministration with ketoconazole *[see Dosage and Administration (2.7) and Drug Interactions (7)]*.

Effect of Combination Therapies:

- Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.

- Cisplatin: Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

- Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

- Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with metastatic castration-resistant prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

- Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed.

Docetaxel was clastogenic in the *in vitro* chromosome aberration test in CHO-K_1 cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about 1/60th to 1/15th the recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

Docetaxel did not reduce fertility in rats when administered in multiple intravenous doses of up to 0.3 mg/kg (about 1/50th the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3rd and 1/15th the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

14 CLINICAL STUDIES

14.1 Locally Advanced or Metastatic Breast Cancer

The efficacy and safety of another formulation of docetaxel has been evaluated in locally advanced or metastatic breast cancer after failure of previous chemotherapy (alkylating agent-containing regimens or anthracycline-containing regimens).

Randomized Trials

In one randomized trial, patients with a history of prior treatment with an anthracycline-containing regimen were assigned to treatment with docetaxel (100 mg/m^2 every 3 weeks) or the combination of mitomycin (12 mg/m^2 every 6 weeks) and vinblastine (6 mg/m^2 every 3 weeks). Two hundred three patients were randomized to docetaxel and 189 to the comparator arm. Most patients had received prior chemotherapy for metastatic disease; only 27 patients on the docetaxel arm and 33 patients on the comparator arm entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The following table summarizes the study results (See Table 12).

Table 12 - Efficacy of Docetaxel in the Treatment of Breast Cancer Patients Previously Treated with an Anthracycline-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	**Docetaxel (n=203)**	**Mitomycin/ Vinblastine (n=189)**	**p-value**
Median Survival	11.4 months	8.7 months	p=0.01 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.73 0.58-0.93		
Median Time to Progression	4.3 months	2.5 months	p=0.01 Log Rank
Risk Ratio*, Progression (Docetaxel: Control) 95% CI (Risk Ratio)	0.75 0.61-0.94		
Overall Response Rate Complete Response Rate	28.1% 3.4%	9.5% 1.6%	p<0.0001 Chi Square

*For the risk ratio, a value less than 1.00 favors docetaxel.

In a second randomized trial, patients previously treated with an alkylating-containing regimen were assigned to treatment with docetaxel (100 mg/m^2) or doxorubicin (75 mg/m^2) every 3 weeks. One hundred sixty-one patients were randomized to docetaxel and 165 patients to doxorubicin. Approximately one-half of patients had received prior chemotherapy for metastatic disease, and one-half entered the study following relapse after adjuvant therapy. Three-quarters of patients had measurable, visceral metastases. The primary endpoint was time to progression. The study results are summarized below (See Table 13).

Table 13 - Efficacy of Docetaxel in the Treatment of Breast Cancer Patients Previously Treated with an Alkylating-Containing Regimen (Intent-to-Treat Analysis)

Efficacy Parameter	Docetaxel (n=161)	Doxorubicin (n=165)	p-value
Median Survival	14.7 months	14.3 months	p=0.39 Log Rank
Risk Ratio*, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.89 0.68-1.16		
Median Time to Progression	6.5 months	5.3 months	p=0.45 Log Rank
Risk Ratio*, Progression (Docetaxel: Control) 95% CI (Risk Ratio)	0.93 0.71-1.16		
Overall Response Rate Complete Response Rate	45.3% 6.8%	29.7% 4.2%	p=0.004 Chi Square

*For the risk ratio, a value less than 1 favors docetaxel.

In another multicenter open-label, randomized trial (TAX313), in the treatment of patients with advanced breast cancer who progressed or relapsed after one prior chemotherapy regimen, 527 patients were randomized to receive docetaxel monotherapy 60 mg/m^2 (n=151), 75 mg/m^2 (n=188) or 100 mg/m^2 (n=188). In this trial, 94% of patients had metastatic disease and 79% had received prior anthracycline therapy. Response rate was the primary endpoint. Response rates increased with docetaxel dose: 19.9% for the 60 mg/m^2 group compared to 22.3% for the 75 mg/m^2 and 29.8% for the 100 mg/m^2 group; pair-wise comparison between the 60 mg/m^2 and 100 mg/m^2 groups was statistically significant (p=0.037).

Single Arm Studies

Docetaxel at a dose of 100 mg/m^2 was studied in six single arm studies involving a total of 309 patients with metastatic breast cancer in whom previous chemotherapy had failed. Among these, 190 patients had anthracycline-resistant breast cancer, defined as progression during an anthracycline-containing chemotherapy regimen for metastatic disease, or relapse during an anthracycline-containing adjuvant regimen. In anthracycline-resistant patients, the overall response rate was 37.9% (72/190; 95% C.I.: 31% to 44.8%) and the complete response rate was 2.1%.

Docetaxel was also studied in three single arm Japanese studies at a dose of 60 mg/m^2, in 174 patients who had received prior chemotherapy for locally advanced or metastatic breast cancer. Among 26 patients whose best response to an anthracycline had been progression, the response rate was 34.6% (95% C.I.: 17.2% to 55.7%), similar to the response rate in single arm studies of 100 mg/m^2.

14.2 Adjuvant Treatment of Breast Cancer

A multicenter, open-label, randomized trial (TAX316) evaluated the efficacy and safety of another formulation of docetaxel for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease. After stratification according to the number of positive lymph nodes (1 to 3, 4+), 1,491 patients were randomized to receive either docetaxel 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC arm). Both regimens were administered every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion; all other drugs were given as intravenous bolus on day 1. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to

guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

Results from a second interim analysis (median follow-up 55 months) are as follows: In study TAX316, the docetaxel-containing combination regimen TAC showed significantly longer disease-free survival (DFS) than FAC (hazard ratio=0.74; 2-sided 95% CI=0.6, 0.92, stratified log rank p=0.0047). The primary endpoint, disease-free survival, included local and distant recurrences, contralateral breast cancer and deaths from any cause. The overall reduction in risk of relapse was 25.7% for TAC-treated patients. (See Figure 1).

At the time of this interim analysis, based on 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95% CI=0.53, 0.9). (See Figure 2). There will be further analysis at the time survival data mature.

Figure 1 - TAX316 Disease Free Survival K-M curve

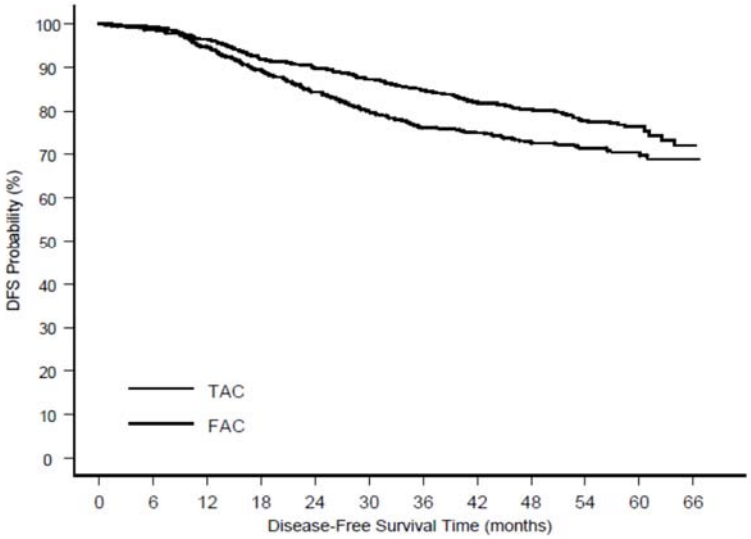
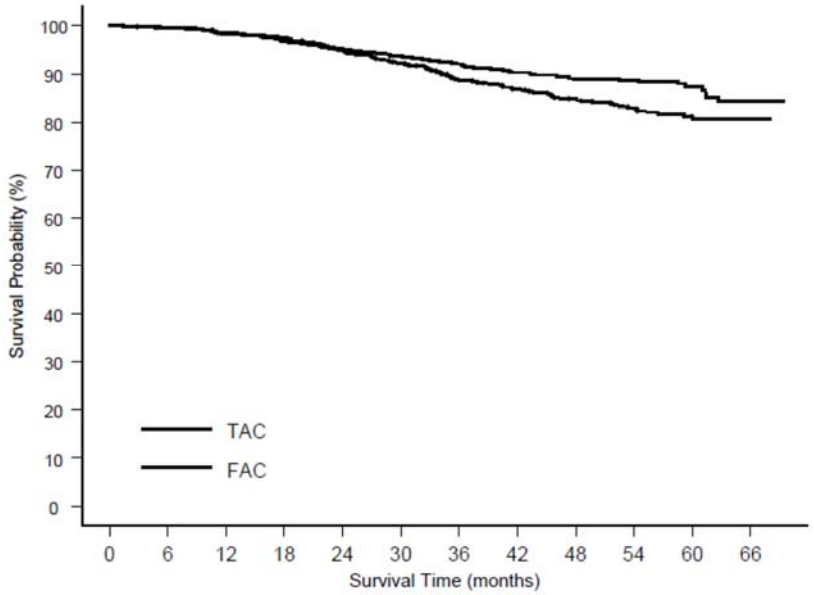


Figure 2 - TAX316 Overall Survival K-M Curve



The following table describes the results of subgroup analyses for DFS and OS (See Table 14).

Table 14 - Subset Analyses-Adjuvant Breast Cancer Study

		Disease Free Survival		Overall Survival	
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**Hazard ratio***	**95% CI**
No. of positive nodes					
Overall	744	0.74	(0.6, 0.92)	0.69	(0.53, 0.9)
1 to 3	467	0.64	(0.47, 0.87)	0.45	(0.29, 0.7)
4+	277	0.84	(0.63, 1.12)	0.93	(0.66, 1.32)
Receptor status					
Positive	566	0.76	(0.59, 0.98)	0.69	(0.48, 0.99)
Negative	178	0.68	(0.48, 0.97)	0.66	(0.44, 0.98)

*a hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival or overall survival compared to FAC.

14.3 Non-Small Cell Lung Cancer (NSCLC)

The efficacy and safety of another formulation of docetaxel has been evaluated in patients with unresectable, locally advanced or metastatic non-small cell lung cancer whose disease has failed prior platinum-based chemotherapy or in patients who are chemotherapy-naive.

Monotherapy with Docetaxel for NSCLC Previously Treated with Platinum-Based Chemotherapy

Two randomized, controlled trials established that a docetaxel dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy (see below). Docetaxel at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used [see *Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5.3)]*.

One trial (TAX317), randomized patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, no history of taxane exposure, and an ECOG performance status ≤ 2 to docetaxel or best supportive care. The primary endpoint of the study was survival. Patients were initially randomized to docetaxel 100 mg/m^2 or best supportive care, but early toxic deaths at this dose led to a dose reduction to docetaxel 75 mg/m^2. A total of 104 patients were randomized in this amended study to either docetaxel 75 mg/m^2 or best supportive care.

In a second randomized trial (TAX320), 373 patients with locally advanced or metastatic non-small cell lung cancer, a history of prior platinum-based chemotherapy, and an ECOG performance status ≤ 2 were randomized to docetaxel 75 mg/m^2, docetaxel 100 mg/m^2 and a treatment in which the investigator chose either vinorelbine 30 mg/m^2 days 1, 8, and 15 repeated every 3 weeks or ifosfamide 2 g/m^2 days 1-3 repeated every 3 weeks. Forty percent of the patients in this study had a history of prior paclitaxel exposure. The primary endpoint was survival in both trials. The efficacy data for the docetaxel 75 mg/m^2 arm and the comparator arms are summarized in Table 15 and Figures 3 and 4 showing the survival curves for the two studies.

Table 15 - Efficacy of Docetaxel in the Treatment of Non-Small Cell Lung Cancer Patients Previously Treated with a Platinum-Based Chemotherapy Regimen (Intent-to-Treat Analysis)

	TAX317		TAX320	
	Docetaxel 75 mg/m² n=55	**Best Supportive Care n=49**	**Docetaxel 75 mg/m² n=125**	**Control (V/I*) n=123**
Overall Survival Log-rank Test	p=0.01		p=0.13	
Risk Ratio††, Mortality (Docetaxel: Control) 95% CI (Risk Ratio)	0.56 (0.35, 0.88)		0.82 (0.63, 1.06)	
Median Survival 95% CI	7.5 months** (5.5, 12.8)	4.6 months (3.7, 6.1)	5.7 months (5.1, 7.1)	5.6 months (4.4, 7.9)
% 1-year Survival 95% CI	37%**† (24, 50)	12% (2, 23)	30%**† (22, 39)	20% (13, 27)
Time to Progression 95% CI	12.3 weeks** (9, 18.3)	7 weeks (6, 9.3)	8.3 weeks (7, 11.7)	7.6 weeks (6.7, 10.1)
Response Rate 95% CI	5.5% (1.1, 15.1)	Not Applicable	5.7% (2.3, 11.3)	0.8% (0, 4.5)

* Vinorelbine/Ifosfamide
**p≤0.05
† uncorrected for multiple comparisons
†† a value less than 1 favors docetaxel.

Only one of the two trials (TAX317) showed a clear effect on survival, the primary endpoint; that trial also showed an increased rate of survival to one year. In the second study (TAX320) the rate of survival at one year favored docetaxel 75 mg/m^2.

Figure 3 - TAX317 Survival K-M Curves - Docetaxel 75 mg/m^2 vs. Best Supportive Care

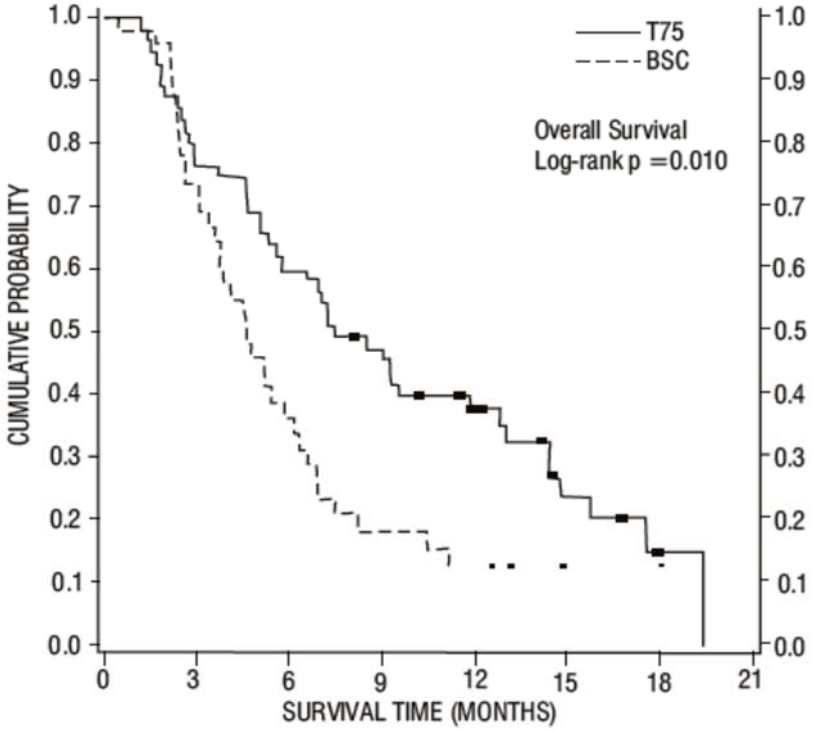
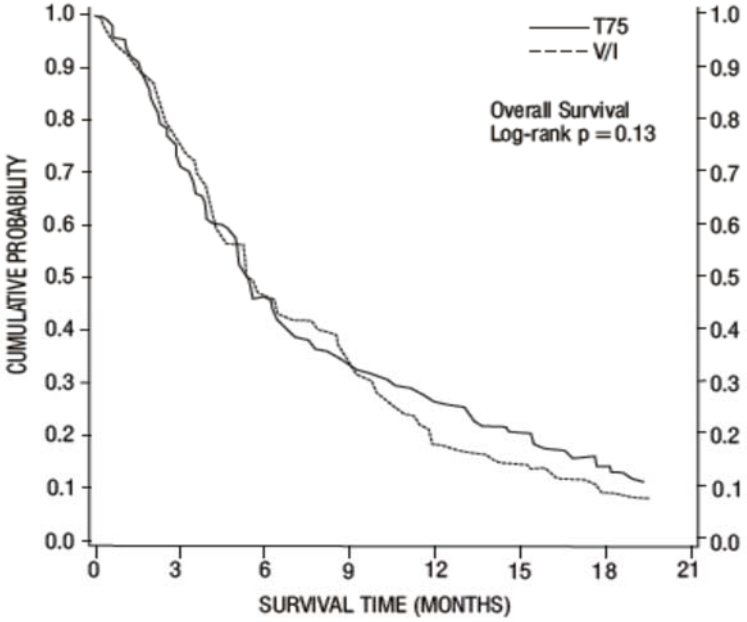


Figure 4 - TAX320 Survival K-M Curves – Docetaxel 75 mg/m^2 vs. Vinorelbine or Ifosfamide Control



Patients treated with docetaxel at a dose of 75 mg/m^2 experienced no deterioration in performance status and body weight relative to the comparator arms used in these trials.

Combination Therapy with Docetaxel for Chemotherapy-Naive NSCLC

In a randomized controlled trial (TAX326), 1218 patients with unresectable stage IIIB or IV NSCLC and no prior chemotherapy were randomized to receive one of three treatments: docetaxel 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin 75 mg/m^2 over 30 to 60 minutes every 3 weeks; vinorelbine 25 mg/m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m^2 administered on day 1 of cycles repeated every 4 weeks; or a combination of docetaxel and carboplatin.

The primary efficacy endpoint was overall survival. Treatment with docetaxel+cisplatin did not result in a statistically significantly superior survival compared to vinorelbine+cisplatin (see table below). The 95% confidence interval of the hazard ratio (adjusted for interim analysis and multiple comparisons) shows that the addition of docetaxel to cisplatin results in an outcome ranging from a 6% inferior to a 26% superior survival compared to the addition of vinorelbine to cisplatin. The results of a further statistical analysis showed that at least (the lower bound of the 95% confidence interval) 62% of the known survival effect of vinorelbine when added to cisplatin (about a 2-month increase in median survival; Wozniak et al. JCO, 1998) was maintained. The efficacy data for the docetaxel+cisplatin arm and the comparator arm are summarized in Table 16.

Table 16 - Survival Analysis of Docetaxel in Combination Therapy for Chemotherapy-Naive NSCLC

Comparison	Docetaxel+Cisplatin n=408	Vinorelbine+Cisplatin n=405
Kaplan-Meier Estimate of Median Survival	10.9 months	10 months
p-value[a]	0.122	
Estimated Hazard Ratio[b]	0.88	
Adjusted 95% CI[c]	(0.74, 1.06)	

[a] From the superiority test (stratified log rank) comparing docetaxel+cisplatin to vinorelbine+cisplatin
[b] Hazard ratio of docetaxel+cisplatin vs. vinorelbine+cisplatin. A hazard ratio of less than 1 indicates that docetaxel+cisplatin is associated with a longer survival.
[c] Adjusted for interim analysis and multiple comparisons.

The second comparison in the same three-arm study, vinorelbine+cisplatin versus docetaxel+carboplatin, did not demonstrate superior survival associated with the docetaxel arm (Kaplan-Meier estimate of median survival was 9.1 months for docetaxel+carboplatin compared to 10.0 months on the vinorelbine+cisplatin arm) and the docetaxel+carboplatin arm did not demonstrate preservation of at least 50% of the survival effect of vinorelbine added to cisplatin. Secondary endpoints evaluated in the trial included objective response and time to progression. There was no statistically significant difference between docetaxel+cisplatin and vinorelbine+cisplatin with respect to objective response and time to progression (see Table 17).

Table 17 - Response and TTP Analysis of Docetaxel in Combination Therapy for Chemotherapy-Naive NSCLC

Endpoint	Docetaxel+Cisplatin	Vinorelbine+Cisplatin	p-value
Objective Response Rate (95% CI)[a]	31.6% (26.5%, 36.8%)	24.4% (19.8%, 29.2%)	Not Significant
Median Time to Progression[b] (95% CI)[a]	21.4 weeks (19.3, 24.6)	22.1 weeks (18.1, 25.6)	Not Significant

[a] Adjusted for multiple comparisons.
[b] Kaplan-Meier estimates.

14.4 Castration-Resistant Prostate Cancer

The safety and efficacy of another formulation of docetaxel in combination with prednisone in patients with metastatic castration-resistant prostate cancer were evaluated in a randomized multicenter active control trial. A total of 1006 patients with Karnofsky Performance Status (KPS) ≥60 were randomized to the following treatment groups:

- Docetaxel 75 mg/m^2 every 3 weeks for 10 cycles.
- Docetaxel 30 mg/m^2 administered weekly for the first 5 weeks in a 6-week cycle for 5 cycles.
- Mitoxantrone 12 mg/m^2 every 3 weeks for 10 cycles.

All 3 regimens were administered in combination with prednisone 5 mg twice daily, continuously.

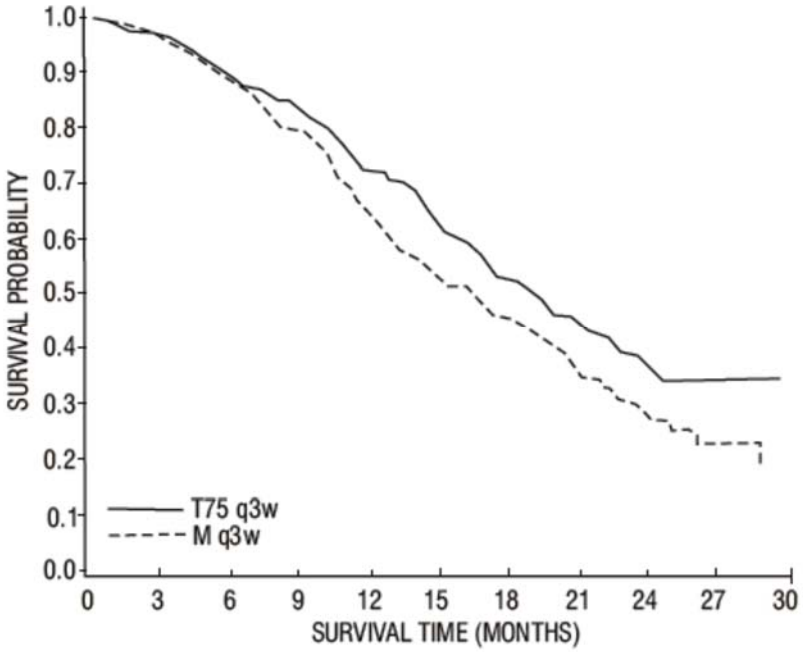
In the docetaxel every three-week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the docetaxel weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the docetaxel every three-week arm versus the control arm are summarized in Table 18 and Figure 5.

Table 18 - Efficacy of Docetaxel in the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer (Intent-to-Treat Analysis)

	Docetaxel+Prednisone every 3 weeks	**Mitoxantrone+Prednisone every 3 weeks**
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	--
95% CI	(0.619-0.936)	--
p-value*	0.0094	--

*Stratified log-rank test. Threshold for statistical significance = 0.0175 because of 3 arms.

Figure 5 - TAX327 Survival K-M Curves



14.5 Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of another formulation of docetaxel for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS >70 were treated with either docetaxel (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and fluorouracil (1,000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1 to 16) for the TCF arm compared to 4 (with a range of 1 to 12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization.

The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19 to 1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 19 and Figures 6 and 7.

Table 19 - Efficacy of Docetaxel (T) in the treatment of patients with gastric adenocarcinoma

Endpoint	**TCF n=221**	**CF n=224**
Median TTP (months) (95%CI)	5.6 (4.86 to 5.91)	3.7 (3.45 to 4.47)
Hazard ratio† (95%CI) *p-value	0.68 (0.55 to 0.84) 0.0004	
Median survival (months) (95%CI)	9.2 (8.38 to 10.58)	8.6 (7.16 to 9.46)
Hazard ratio† (95%CI) *p-value	0.77 (0.62 to 0.96) 0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	

*Unstratified log-rank test

†For the hazard ratio (TCF/CF), values less than 1 favor the docetaxel arm.

Subgroup analyses were consistent with the overall results across age, gender and race.

Figure 6 - Gastric Cancer Study (TAX325) Time to Progression K-M Curve

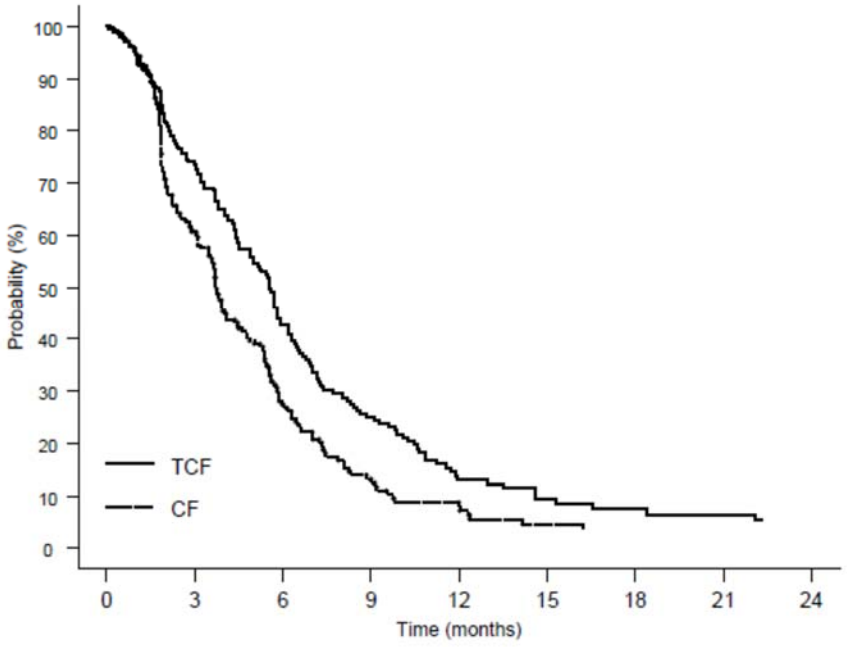
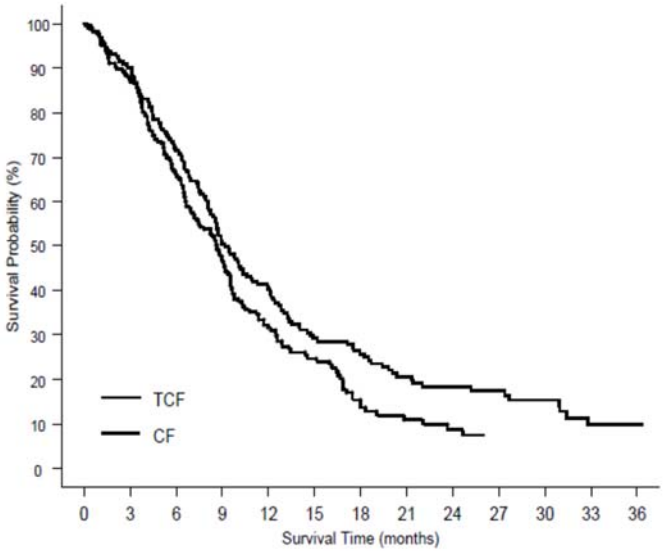


Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve



14.6 Head and Neck Cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of another formulation of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 on Day 1, followed by fluorouracil (F) 750 mg/m^2 per day as a continuous infusion on Days 1 to 5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m^2 on Day 1, followed by fluorouracil (F) 1,000 mg/m^2/day as a continuous infusion on Days 1 to 5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction regimen (1.8 Gy to 2 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after radiotherapy.

The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0077 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow-up time of 33.7 months. Median overall survival with a median follow-up of 51.2 months was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.2 months respectively). Efficacy results are presented in Table 20 and Figures 8 and 9.

Table 20 - Efficacy of Docetaxel in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

ENDPOINT	Docetaxel + Cisplatin+ Fluorouracil n=177	Cisplatin+ Fluorouracil n=181
Median progression free survival (months) (95%CI)	11.4 (10.1 to 14)	8.3 (7.4 to 9.1)
Adjusted Hazard ratio (95%CI) *p-value	0.71 (0.56 to 0.91) 0.0077	
Median survival (months) (95%CI)	18.6 (15.7 to 24)	14.2 (11.5 to 18.7)
Hazard ratio (95%CI) **p-value	0.71 (0.56 to 0.9) 0.0055	
Best overall response (CR + PR) to chemotherapy (%) (95%CI)	67.8 (60.4 to 74.6)	53.6 (46 to 61)
***p-value	0.006	
Best overall response (CR + PR) to study treatment [chemotherapy +/-radiotherapy] (%) (95%CI)	72.3 (65.1 to 78.8)	58.6 (51 to 65.8)
***p-value	0.006	

A Hazard ratio of less than 1 favors Docetaxel+Cisplatin+Fluorouracil
* Stratified log-rank test based on primary tumor site
** Stratified log-rank test, not adjusted for multiple comparisons
*** Chi square test, not adjusted for multiple comparisons

Figure 8 - TAX323 Progression-Free Survival K-M Curve

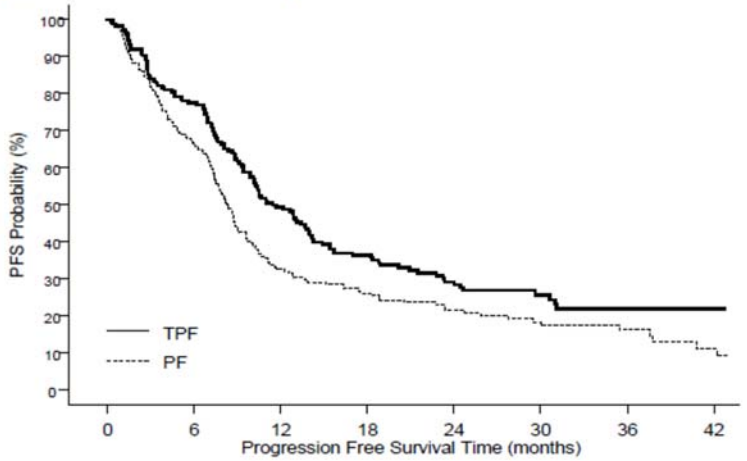
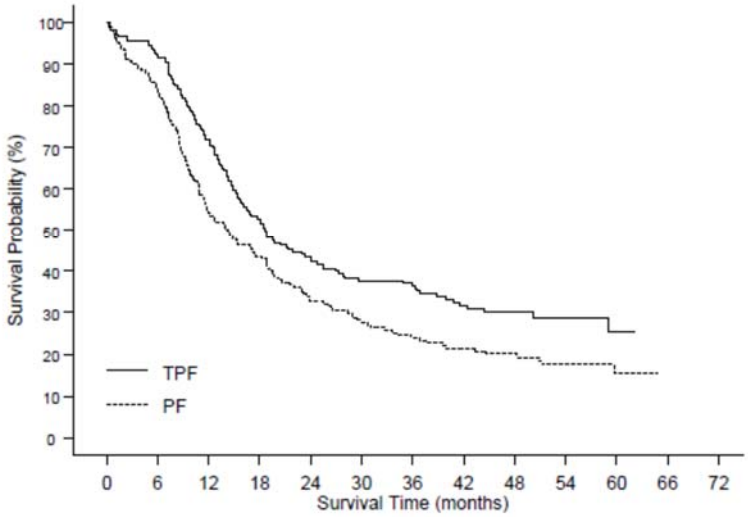


Figure 9 - TAX323 Overall Survival K-M Curve



Induction chemotherapy followed by chemoradiotherapy (TAX324)

The safety and efficacy of another formulation of docetaxel in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomized, multicenter open-label trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1,000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1,000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles.

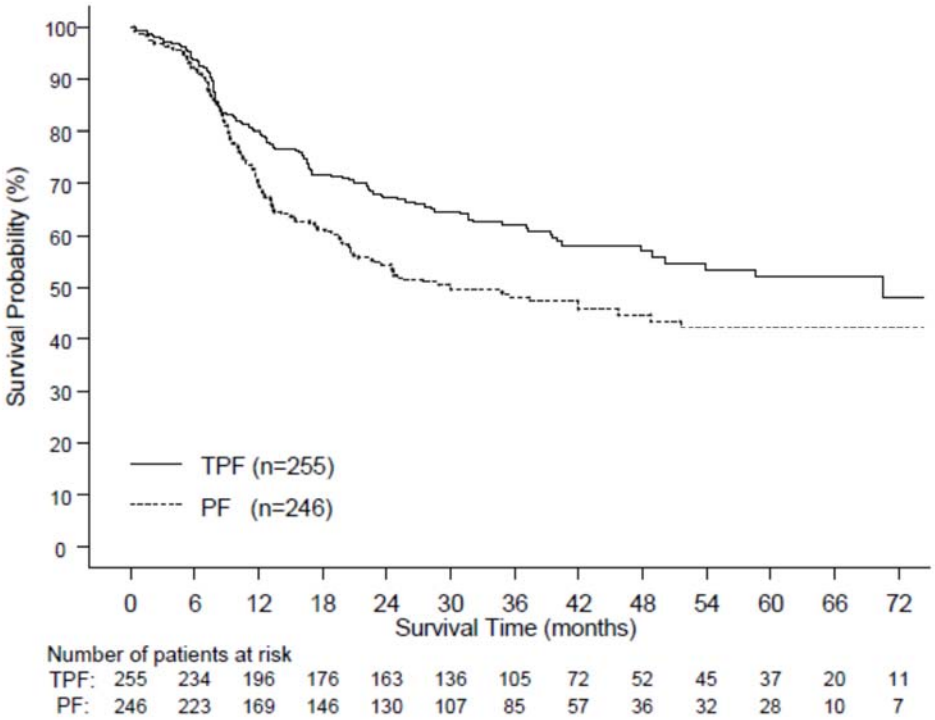
All patients in both treatment arms who did not have progressive disease were to receive 7 weeks of chemoradiotherapy (CRT) following induction chemotherapy 3 to 8 weeks after the start of the last cycle. During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at any time following completion of CRT. The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the docetaxel-containing regimen compared to PF [median OS: 70.6 vs 30.1 months respectively, hazard ratio (HR)=0.7, 95% confidence interval (CI)= 0.54 – 0.9]. Overall survival results are presented in Table 21 and Figure 10.

Table 21 - Efficacy of Docetaxel in the induction treatment of patients with locally advanced SCCHN (Intent-to-Treat Analysis)

ENDPOINT	**Docetaxel + Cisplatin + Fluorouracil n=255**	**Cisplatin + Fluorouracil n=246**
Median overall survival (months) (95% CI)	70.6 (49 to NE)	30.1 (20.9 to 51.5)
Hazard ratio: (95% CI) *p-value	0.7 (0.54 to 0.9) 0.0058	

A Hazard ratio of less than 1 favors docetaxel+cisplatin+fluorouracil
* un-adjusted log-rank test
NE - not estimable

Figure 10 - TAX324 Overall Survival K-M Curve



15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DOCETAXEL INJECTION is supplied in single-dose vials for 20 mg/ mL and single-dose vials for 80 mg/4 mL and 160 mg/8 mL as a sterile, pyrogen-free, non-aqueous solution.

DOCETAXEL INJECTION 20 mg/-mL: NDC 47335-323-40
The vial is in a blister pack in one carton.

DOCETAXEL INJECTION 80 mg/4 mL: NDC 47335-895-40
The vial is in a blister pack in one carton.

DOCETAXEL INJECTION 160 mg/8 mL: NDC 47335-939-40

The vial is in a blister pack in one carton.

16.2 Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. Retain in the original package to protect from bright light.

16.3 Handling and Disposal

Follow procedures for proper handling and disposal of anticancer drugs.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Bone Marrow Suppression
Explain the significance of routine blood cell counts. Thus, it is important that periodic assessment of their blood count be performed to detect the development of neutropenia, thrombocytopenia and/ or anemia *[see Contraindications (4) and Warnings and Precautions (5.3)]*. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.

Gastrointestinal Events, Eye Disorders
Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, excessive tearing and/or vision disturbances are associated with docetaxel administration *[see Adverse Reactions (6)]*. Tell patients to immediately report abdominal pain or tenderness, and/or diarrhea, with or without fever *[see Warnings and Precautions (5.4)]*, any vision changes *[see Warnings and Precautions (5.10)]*.

Hypersensitivity Reactions
Obtain detailed allergy information from the patient prior to DOCETAXEL INJECTION administration. Instruct patients to immediately report signs of a hypersensitivity reaction. Ask patients whether they have previously received paclitaxel therapy, and if they have experienced a hypersensitivity reaction to paclitaxel *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Fluid Retention
Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea and instruct patients to immediately report them *[see Warnings and Precautions (5.6)]*.

Myalgia, Cutaneous Reactions, Neurologic Reactions, Local Site Reactions, Fatigue, Alopecia
Instruct patients to report myalgia *[see Adverse Reactions (6)]*, cutaneous reactions *[see Warnings and Precautions (5.8)]*, neurologic reactions *[see Warnings and Precautions (5.9)]*, or infusion site reactions *[see Adverse Reactions (6)]*. Explain to patients that side effects such as fatigue and hair loss (cases of permanent hair loss have been reported) are associated with docetaxel administration *[see Adverse Reactions (6)]*.

Cardiac disorders
Tell patients to report any irregular and/or rapid heartbeat, severe shortness of breath, dizziness, and/or fainting *[see Adverse Reactions (6)]*.

Importance of Corticosteroids
Explain the significance of oral corticosteroids such as dexamethasone administration to the patient to help facilitate compliance. Instruct patients to report if they were not compliant with oral corticosteroid regimen *[see Dosage and Administration (2.6)]*.

Alcohol Content in DOCETAXEL INJECTION
Explain to patients the possible effects of the alcohol content in DOCETAXEL INJECTION, including possible effects on the central nervous system *[see Warnings and Precautions (5.12)]*.

Ability to Drive or Operate Machines
Explain to patients that DOCETAXEL INJECTION may impair their ability to drive or operate machines due to its side effects *[see Adverse Reactions (6)]* or due to the alcohol content of DOCETAXEL INJECTION *[see Warnings and Precautions (5.12)]*. *Advise* them not to drive or use machines if they experience these side effects during treatment.

Drug Interactions

Inform patients about the risk of drug interactions and the importance of providing a list of prescription and non-prescription drugs to their healthcare provider *[see Drug Interactions (7)]*.

Embryo-Fetal Toxicity

DOCETAXEL INJECTION can cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Advise female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of DOCETAXEL INJECTION. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of DOCETAXEL INJECTION *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment and for 2 weeks after the last dose of DOCETAXEL INJECTION *[see Use in Specific Populations (8.2)]*.

Patient Information

DOCETAXEL (doe-se-TAKS-el) INJECTION

for intravenous use

Read this Patient Information before you receive your first treatment with DOCETAXEL INJECTION and each time before you are treated. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about DOCETAXEL INJECTION?

DOCETAXEL INJECTION can cause serious side effects, including death.

- **The chance of death in people who receive DOCETAXEL INJECTION is higher if you:**
  - have liver problems
  - receive high doses of DOCETAXEL INJECTION
  - have non-small cell lung cancer and have been treated with chemotherapy medicines that contain platinum
- **DOCETAXEL INJECTION can affect your blood cells.** Your healthcare provider should do routine blood tests during treatment with DOCETAXEL INJECTION. This will include regular checks of your white blood cell counts. If your white blood cells are too low, your healthcare provider may not treat you with DOCETAXEL INJECTION until you have enough white blood cells. People with low white blood cell counts can develop life-threatening infections. The earliest sign of infection may be fever. Follow your healthcare provider's instructions for how often to take your temperature during treatment with DOCETAXEL INJECTION. Call your healthcare provider right away if you have a fever.
- **Swelling (inflammation) of the small intestine and colon.** This can happen at any time and could lead to death as early as the first day you get symptoms. Tell your healthcare provider right away if you develop new or worse symptoms of intestinal problems, including stomach (abdominal) pain or tenderness, diarrhea, or fever.
- **Severe allergic reactions** are medical emergencies that can happen in people who receive DOCETAXEL INJECTION and can lead to death. You may be at risk of developing a severe allergic reaction to DOCETAXEL INJECTION if you are allergic to paclitaxel. Your healthcare provider will monitor you closely for allergic reactions during your DOCETAXEL INJECTION infusion.

  Tell your healthcare provider right away if you have any of these signs of a severe allergic reaction:
  - trouble breathing
  - sudden swelling of your face, lips, tongue, throat, or trouble swallowing
  - hives (raised bumps), rash, or redness all over your body
- **Your body may hold too much fluid (severe fluid retention)** during treatment with DOCETAXEL INJECTION. This can be life threatening. To decrease the chance of this happening, you must take another medicine, a corticosteroid, before each DOCETAXEL INJECTION treatment. You must take the corticosteroid exactly as your healthcare provider tells you. Tell your healthcare provider or nurse before your DOCETAXEL INJECTION treatment if you forgot to take your corticosteroid dose or do not take it as your healthcare provider tells you. Tell your healthcare provider right away if you have swelling in your legs or feet, weight gain or shortness of breath.

What is DOCETAXEL INJECTION?

DOCETAXEL INJECTION is a prescription anti-cancer medicine used to treat certain people with:

- breast cancer
- non-small cell lung cancer
- prostate cancer
- stomach cancer
- head and neck cancer

It is not known if DOCETAXEL INJECTION is effective in children.

Do not receive DOCETAXEL INJECTION if you:

- have a low white blood cell count.
- have had a severe allergic reaction to:
  - docetaxel, the active ingredient in DOCETAXEL INJECTION, or
  - any other medicines that contain polysorbate 80. Ask your healthcare provider or pharmacist if you are not sure.

  See "**What is the most important information I should know about DOCETAXEL INJECTION?**" for the signs and symptoms of a severe allergic reaction.

  See the end of this Patient Information for a complete list of the ingredients in DOCETAXEL INJECTION.

Before you receive DOCETAXEL INJECTION, tell your healthcare provider about all of your medical conditions, including if you:

- are allergic to any medicines, including paclitaxel. See "**Do not receive DOCETAXEL INJECTION if you**".
- have liver problems

- are pregnant or plan to become pregnant. DOCETAXEL INJECTION can harm your unborn baby. You should not become pregnant during treatment with DOCETAXEL INJECTION.

  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start treatment with DOCETAXEL INJECTION.
  - You should use effective birth control (contraception) during treatment with DOCETAXEL INJECTION and for 6 months after the last dose.

  Males with female partners who are able to become pregnant should use effective birth control during treatment with DOCETAXEL INJECTION and for 3 months after the last dose.

  Talk to your healthcare provider if you have questions about birth control options that are right for you.
- are breastfeeding or plan to breastfeed. It is not known if DOCETAXEL INJECTION passes into your breast milk. Do not breastfeed during treatment with DOCETAXEL INJECTION and for 2 weeks after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. DOCETAXEL INJECTION may affect the way other medicines work, and other medicines may affect the way DOCETAXEL INJECTION works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive DOCETAXEL INJECTION?

- DOCETAXEL INJECTION will be given to you as an intravenous (IV) injection into your vein, usually over 1 hour.
- DOCETAXEL INJECTION is usually given every 3 weeks.
- Your healthcare provider will decide how long you will receive treatment with DOCETAXEL INJECTION.
- Your healthcare provider will check your blood cell counts and other blood tests during your treatment with DOCETAXEL INJECTION to check for side effects of DOCETAXEL INJECTION.
- Your healthcare provider may stop your treatment, change the timing of your treatment, or change the dose of your treatment if you have certain side effects while receiving DOCETAXEL INJECTION.

What are the possible side effects of DOCETAXEL INJECTION?

DOCETAXEL INJECTION may cause serious side effects including death.

- See "**What is the most important information I should know about DOCETAXEL INJECTION?**"
- **Acute Myeloid Leukemia (AML)**, a type of blood cancer, can happen in people who receive DOCETAXEL INJECTION along with certain other medicines.
- **Other blood disorders.** Changes in blood counts due to leukemia and other blood disorders may occur years after treatment with DOCETAXEL INJECTION.
- **Skin reactions** including redness and swelling of your arms and legs with peeling of your skin. Tell your healthcare provider if you are having a skin reaction.
- **Neurologic problems.** Neurologic symptoms are common in people who receive DOCETAXEL INJECTION but can be severe. Tell your healthcare provider if you have numbness, tingling, or burning in your hands or feet (peripheral neuropathy) or weakness of your legs, feet, arms, or hands (motor weakness).
- **Vision problems** including blurred vision or loss of vision. Tell your healthcare provider right away if you have any vision changes.
- **DOCETAXEL INJECTION contains alcohol.** The alcohol content in DOCETAXEL INJECTION may impair your ability to drive or use machinery right after receiving DOCETAXEL INJECTION. Consider whether you should drive, operate machinery or do other dangerous activities right after you receive DOCETAXEL INJECTION treatment.
- You may experience side effects of this medicine that may impair your ability to drive, use tools, or operate machines. If this happens, do not drive or use any tools or machines before discussing with your healthcare provider.

The most common side effects of DOCETAXEL INJECTION include:

- infections
- low white blood cells (help fight infections), low red blood cells (anemia) and low platelets (help blood to clot)
- allergic reactions (See "**What is the most important information I should know about DOCETAXEL INJECTION?**")
- changes in your sense of taste
- shortness of breath
- constipation
- decreased appetite
- changes in your fingernails or toenails
- swelling of your hands, face or feet
- feeling weak or tired
- joint and muscle pain
- nausea and vomiting
- diarrhea
- mouth or lips sores
- hair loss: in some people, permanent hair loss has been reported
- redness of the eye, excess tearing
- skin reactions at the site of DOCETAXEL INJECTION administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin
- tissue damage if DOCETAXEL INJECTION leaks out of the vein into the tissues

Tell your healthcare provider if you have a fast or irregular heartbeat, severe shortness of breath, dizziness or fainting during your infusion. If any of these events occurs after your infusion, get medical help right away.

These are not all the possible side effects of DOCETAXEL INJECTION. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of DOCETAXEL INJECTION.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information. You can ask your pharmacist or healthcare provider for information about DOCETAXEL INJECTION that is written for health professionals.

What are the ingredients in DOCETAXEL INJECTION?

Active ingredient: docetaxel

Inactive ingredients: citric acid anhydrous, polysorbate 80 and dehydrated alcohol solution

Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512
Manufactured by: Sun Pharmaceutical Ind. Ltd. Halol-Baroda Highway, Halol-389 350, Gujarat, India.
PJPI0558

For more information call 1-800-818-4555.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2019

Every three-week injection of DOCETAXEL INJECTION for breast, non-small cell lung and stomach, and head and neck cancers.
Take your oral corticosteroid medicine as your healthcare provider tells you.
Oral corticosteroid dosing:

Day 1 Date:_____ Time:_____AM _____PM

Day 2 Date:_____ Time:_____AM _____PM
(DOCETAXEL INJECTION Treatment Day)

Day 3 Date:_____ Time:_____AM _____PM

Every three-week injection of DOCETAXEL INJECTION for prostate cancer.
Take your oral corticosteroid medicine as your healthcare provider tells you.
Oral corticosteroid dosing:

Date:_____ Time:_____

Date:_____ Time:_____
(DOCETAXEL INJECTION Treatment Day)

Time:_____