| **Adverse Reaction** | **Docetaxel 75 mg/m$^2$ + Cisplatin 75 mg/m$^2$ n=406 %** | **Vinorelbine 25 mg/m$^2$ + Cisplatin 100 mg/m$^2$ n=396 %** |
|---|---|---|
| **Neutropenia** | | |
| Any | 91 | 90 |
| Grade 3/4 | 74 | 78 |
| **Febrile Neutropenia** | 5 | 5 |
| **Thrombocytopenia** | | |
| Any | 15 | 15 |
| Grade 3/4 | 3 | 4 |
| **Anemia** | | |
| Any | 89 | 94 |
| Grade 3/4 | 7 | 25 |
| **Infection** | | |
| Any | 35 | 37 |
| Grade 3/4 | 8 | 8 |
| **Fever in absence of infection** | | |
| Any | 33 | 29 |
| Grade 3/4 | <1 | 1 |
| **Hypersensitivity Reaction*** | | |
| Any | 12 | 4 |
| Grade 3/4 | 3 | <1 |
| **Fluid Retention**** | | |
| Any | 54 | 42 |
| All severe or life-threatening events | 2 | 2 |
| Pleural effusion | | |
| Any | 23 | 22 |
| All severe or life-threatening events | 2 | 2 |
| Peripheral edema | | |
| Any | 34 | 18 |
| All severe or life-threatening events | <1 | <1 |
| Weight gain | | |
| Any | 15 | 9 |
| All severe or life-threatening events | <1 | <1 |
| **Neurosensory** | | |

| | | |
|---|---|---|
| Any | 47 | 42 |
| Grade 3/4 | 4 | 4 |
| **Neuromotor** | | |
| Any | 19 | 17 |
| Grade 3/4 | 3 | 6 |
| **Skin** | | |
| Any | 16 | 14 |
| Grade 3/4 | <1 | 1 |
| **Nausea** | | |
| Any | 72 | 76 |
| Grade 3/4 | 10 | 17 |
| **Vomiting** | | |
| Any | 55 | 61 |
| Grade 3/4 | 8 | 16 |
| **Diarrhea** | | |
| Any | 47 | 25 |
| Grade 3/4 | 7 | 3 |
| **Anorexia**** | | |
| Any | 42 | 40 |
| All severe or life-threatening events | 5 | 5 |
| **Stomatitis** | | |
| Any | 24 | 21 |
| Grade 3/4 | 2 | 1 |
| **Alopecia** | | |
| Any | 75 | 42 |
| Grade 3 | <1 | 0 |
| **Asthenia**** | | |
| Any | 74 | 75 |
| All severe or life-threatening events | 12 | 14 |
| **Nail Disorder**** | | |
| Any | 14 | <1 |
| All severe events | <1 | 0 |
| **Myalgia**** | | |
| Any | 18 | 12 |
| All severe events | <1 | <1 |

* Replaces NCI term "Allergy"
** COSTART term and grading system

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2%) in the vinorelbine+cisplatin arm.

The second comparison in the study, vinorelbine+cisplatin versus docetaxel+carboplatin (which did not demonstrate a superior survival associated with docetaxel, *[see Clinical Studies (14.3)]*) demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the docetaxel+carboplatin arm, while a higher incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Prostate Cancer

*Combination therapy with docetaxel in patients with prostate cancer*

The following data are based on the experience of 332 patients, who were treated with docetaxel 75 mg/m$^2$ every 3 weeks in combination with prednisone 5 mg orally twice daily (see **Table 9**).

**Table 9 - Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer who Received Docetaxel in Combination with Prednisone (TAX327)**

| | **Docetaxel 75 mg/m$^2$ every 3 weeks + prednisone 5 mg twice daily n=332 %** | | **Mitoxantrone 12 mg/m$^2$ every 3 weeks + prednisone 5 mg twice daily n=335 %** | |
|---|---|---|---|---|
| **Adverse Reaction** | **Any** | **Grade 3/4** | **Any** | **Grade 3/4** |
| **Anemia** | 67 | 5 | 58 | 2 |
| **Neutropenia** | 41 | 32 | 48 | 22 |
| **Thrombocytopenia** | 3 | 1 | 8 | 1 |
| **Febrile neutropenia** | 3 | N/A | 2 | N/A |
| **Infection** | 32 | 6 | 20 | 4 |
| **Epistaxis** | 6 | 0 | 2 | 0 |
| **Allergic Reactions** | 8 | 1 | 1 | 0 |
| **Fluid Retention*** | 24 | 1 | 5 | 0 |
| Weight Gain* | 8 | 0 | 3 | 0 |
| Peripheral Edema* | 18 | 0 | 2 | 0 |

| | | | | |
|---|---|---|---|---|
| **Neuropathy Sensory** | 30 | 2 | 7 | 0 |
| **Neuropathy Motor** | 7 | 2 | 3 | 1 |
| **Rash/Desquamation** | 6 | 0 | 3 | 1 |
| **Alopecia** | 65 | N/A | 13 | N/A |
| **Nail Changes** | 30 | 0 | 8 | 0 |
| **Nausea** | 41 | 3 | 36 | 2 |
| **Diarrhea** | 32 | 2 | 10 | 1 |
| **Stomatitis/Pharyngitis** | 20 | 1 | 8 | 0 |
| **Taste Disturbance** | 18 | 0 | 7 | 0 |
| **Vomiting** | 17 | 2 | 14 | 2 |
| **Anorexia** | 17 | 1 | 14 | 0 |
| **Cough** | 12 | 0 | 8 | 0 |
| **Dyspnea** | 15 | 3 | 9 | 1 |
| **Cardiac left ventricular function** | 10 | 0 | 22 | 1 |
| **Fatigue** | 53 | 5 | 35 | 5 |
| **Myalgia** | 15 | 0 | 13 | 1 |
| **Tearing** | 10 | 1 | 2 | 0 |
| **Arthralgia** | 8 | 1 | 5 | 1 |

*Related to treatment

Gastric Cancer

*Combination therapy with docetaxel in gastric adenocarcinoma*

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with docetaxel 75 mg/m$^2$ in combination with cisplatin and fluorouracil (see **Table 10**).

**Table 10 - Clinically Important Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study**

| | **Docetaxel 75 mg/m$^2$ + cisplatin 75 mg/m$^2$ + fluorouracil 750 mg/m$^2$ n=221** | | **Cisplatin 100 mg/m$^2$ + fluorouracil 1000 mg/m$^2$ n=224** | |
|---|---|---|---|---|
| **Adverse Reaction** | **Any %** | **Grade 3/4 %** | **Any %** | **Grade 3/4 %** |
| **Anemia** | 97 | 18 | 93 | 26 |
| **Neutropenia** | 96 | 82 | 83 | 57 |
| **Fever in the absence of infection** | 36 | 2 | 23 | 1 |

| | | | | |
|---|---|---|---|---|
| **Thrombocytopenia** | 26 | 8 | 39 | 14 |
| **Infection** | 29 | 16 | 23 | 10 |
| **Febrile neutropenia** | 16 | N/A | 5 | N/A |
| **Neutropenic infection** | 16 | N/A | 10 | N/A |
| **Allergic reactions** | 10 | 2 | 6 | 0 |
| **Fluid retention*** | 15 | 0 | 4 | 0 |
| **Edema*** | 13 | 0 | 3 | 0 |
| **Lethargy** | 63 | 21 | 58 | 18 |
| **Neurosensory** | 38 | 8 | 25 | 3 |
| **Neuromotor** | 9 | 3 | 8 | 3 |
| **Dizziness** | 16 | 5 | 8 | 2 |
| **Alopecia** | 67 | 5 | 41 | 1 |
| **Rash/itch** | 12 | 1 | 9 | 0 |
| **Nail changes** | 8 | 0 | 0 | 0 |
| **Skin desquamation** | 2 | 0 | 0 | 0 |
| **Nausea** | 73 | 16 | 76 | 19 |
| **Vomiting** | 67 | 15 | 73 | 19 |
| **Anorexia** | 51 | 13 | 54 | 12 |
| **Stomatitis** | 59 | 21 | 61 | 27 |
| **Diarrhea** | 78 | 20 | 50 | 8 |
| **Constipation** | 25 | 2 | 34 | 3 |
| **Esophagitis/dysphagia/ odynophagia** | 16 | 2 | 14 | 5 |
| **Gastrointestinal pain/cramping** | 11 | 2 | 7 | 3 |
| **Cardiac dysrhythmias** | 5 | 2 | 2 | 1 |
| **Myocardial ischemia** | 1 | 0 | 3 | 2 |
| **Tearing** | 8 | 0 | 2 | 0 |
| **Altered hearing** | 6 | 0 | 13 | 2 |

Clinically important treatment emergent adverse reactions were determined based upon frequency, severity, and clinical impact of the adverse reaction.
*Related to treatment

Head and Neck Cancer
*Combination therapy with docetaxel in head and neck cancer*

**Table 11** summarizes the safety data obtained from patients that received induction chemotherapy with docetaxel 75 mg/m$^2$ in combination with cisplatin and fluorouracil followed by radiotherapy (TAX323; 174 patients) or chemoradiotherapy (TAX324; 251 patients). The treatment regimens are described in Section 14.6.

**Table 11 - Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with SCCHN Receiving Induction Chemotherapy with**

**Docetaxel in Combination with Cisplatin and Fluorouracil Followed by Radiotherapy (TAX323) or Chemoradiotheraphy (TAX324)**

| | TAX323 (n=355) | | | | TAX324 (n=494) | | | |
|---|---|---|---|---|---|---|---|---|
| | Docetaxel arm (n=174) | | Comparator arm (n=181) | | Docetaxel arm (n=251) | | Comparator arm (n=243) | |
| **Adverse Reaction** (by Body System) | **Any %** | **Grade 3/4 %** | **Any %** | **Grade 3/4 %** | **Any %** | **Grade 3/4 %** | **Any %** | **Grade 3/4 %** |
| **Neutropenia** | 93 | 76 | 87 | 53 | 95 | 84 | 84 | 56 |
| **Anemia** | 89 | 9 | 88 | 14 | 90 | 12 | 86 | 10 |
| **Thrombocytopenia** | 24 | 5 | 47 | 18 | 28 | 4 | 31 | 11 |
| **Infection** | 27 | 9 | 26 | 8 | 23 | 6 | 28 | 5 |
| **Febrile neutropenia*** | 5 | N/A | 2 | N/A | 12 | N/A | 7 | N/A |
| **Neutropenic infection** | 14 | N/A | 8 | N/A | 12 | N/A | 8 | N/A |
| **Cancer pain** | 21 | 5 | 16 | 3 | 17 | 9 | 20 | 11 |
| **Lethargy** | 41 | 3 | 38 | 3 | 61 | 5 | 56 | 10 |
| **Fever in the absence of infection** | 32 | 1 | 37 | 0 | 30 | 4 | 28 | 3 |
| **Myalgia** | 10 | 1 | 7 | 0 | 7 | 0 | 7 | 2 |
| **Weight loss** | 21 | 1 | 27 | 1 | 14 | 2 | 14 | 2 |
| **Allergy** | 6 | 0 | 3 | 0 | 2 | 0 | 0 | 0 |
| **Fluid retention**** | 20 | 0 | 14 | 1 | 13 | 1 | 7 | 2 |
| **Edema only** | 13 | 0 | 7 | 0 | 12 | 1 | 6 | 1 |
| **Weight gain only** | 6 | 0 | 6 | 0 | 0 | 0 | 1 | 0 |
| **Dizziness** | 2 | 0 | 5 | 1 | 16 | 4 | 15 | 2 |
| **Neurosensory** | 18 | 1 | 11 | 1 | 14 | 1 | 14 | 0 |
| **Altered hearing** | 6 | 0 | 10 | 3 | 13 | 1 | 19 | 3 |
| **Neuromotor** | 2 | 1 | 4 | 1 | 9 | 0 | 10 | 2 |
| **Alopecia** | 81 | 11 | 43 | 0 | 68 | 4 | 44 | 1 |
| **Rash/itch** | 12 | 0 | 6 | 0 | 20 | 0 | 16 | 1 |
| **Dry skin** | 6 | 0 | 2 | 0 | 5 | 0 | 3 | 0 |
| **Desquamation** | 4 | 1 | 6 | 0 | 2 | 0 | 5 | 0 |
| **Nausea** | 47 | 1 | 51 | 7 | 77 | 14 | 80 | 14 |
| **Stomatitis** | 43 | 4 | 47 | 11 | 66 | 21 | 68 | 27 |
| **Vomiting** | 26 | 1 | 39 | 5 | 56 | 8 | 63 | 10 |
| **Diarrhea** | 33 | 3 | 24 | 4 | 48 | 7 | 40 | 3 |
| **Constipation** | 17 | 1 | 16 | 1 | 27 | 1 | 38 | 1 |
| **Anorexia** | 16 | 1 | 25 | 3 | 40 | 12 | 34 | 12 |
| **Esophagitis/dysphagia /Odynophagia** | 13 | 1 | 18 | 3 | 25 | 13 | 26 | 10 |
| **Taste, sense of smell altered** | 10 | 0 | 5 | 0 | 20 | 0 | 17 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Gastrointestinal pain/cramping** | 8 | 1 | 9 | 1 | 15 | 5 | 10 | 2 |
| **Heartburn** | 6 | 0 | 6 | 0 | 13 | 2 | 13 | 1 |
| **Gastrointestinal bleeding** | 4 | 2 | 0 | 0 | 5 | 1 | 2 | 1 |
| **Cardiac dysrhythmia** | 2 | 2 | 2 | 1 | 6 | 3 | 5 | 3 |
| **Venous*** ** | 3 | 2 | 6 | 2 | 4 | 2 | 5 | 4 |
| **Ischemia myocardial** | 2 | 2 | 1 | 0 | 2 | 1 | 1 | 1 |
| **Tearing** | 2 | 0 | 1 | 0 | 2 | 0 | 2 | 0 |
| **Conjunctivitis** | 1 | 0 | 1 | 0 | 1 | 0 | 0.4 | 0 |

Clinically important treatment emergent adverse reactions based upon frequency, severity, and clinical impact.
*Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
**Related to treatment.
*** Includes superficial and deep vein thrombosis and pulmonary embolism

### 6.2 Post-marketing Experiences

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

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

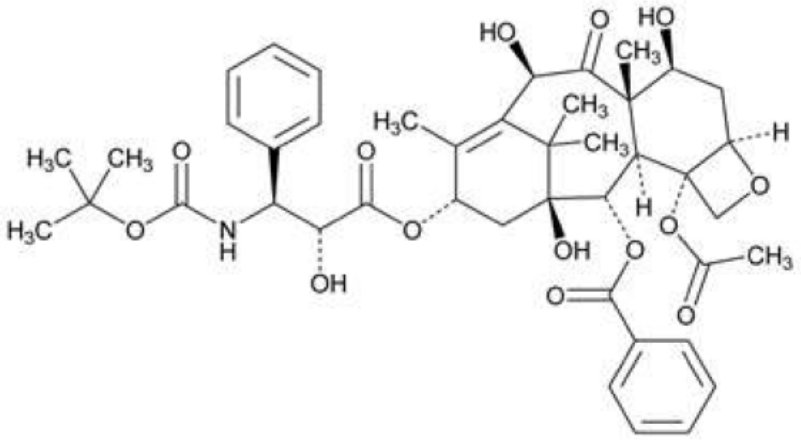
There is no known antidote for Docetaxel Injection overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients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



Docetaxel 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.

Docetaxel Injection is a clear, colorless to pale yellow solution. Docetaxel Injection is sterile, non-pyrogenic, and is available in multiple dose vials, supplied as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.

Each mL of Docetaxel Injection contains 10 mg docetaxel, 275.9 mg alcohol 96% (v/v), 4 mg citric acid, 648 mg polyethylene glycol 300, and 80 mg polysorbate 80.

## 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 Human 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 $\gamma$ 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 $\alpha_1$-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.

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 Injection. 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.

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 co-administration with ketoconazole *[see Dosage and Administration (2.7) and Drug-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 hormone-refractory metastatic 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 1/60$^{th}$ to 1/15$^{th}$ 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 1/50$^{th}$ 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 docetaxel have 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) | 0.73 | | |
| 95% CI (Risk Ratio) | 0.58-0.93 | | |
| Median Time to Progression | 4.3 months | 2.5 months | p=0.01 Log Rank |
| Risk Ratio*, Progression (Docetaxel: Control) | 0.75 | | p=0.01 Log Rank |
| 95% CI (Risk Ratio) | 0.61-0.94 | | |
| Overall Response Rate | 28.1% | 9.5% | p<0.000 1 Chi Square |
| Complete Response Rate | 3.4% | 1.6% | |

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

*For the risk ratio, a value less than 1.00 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.: 31.0-44.8) 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.: 17.2-55.7), 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 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 (1-3, 4+), 1491 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 cyclosphosphamide 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=0.60, 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, 0.90). (See **Figure 2**). There will be further analysis at the time survival data mature.

**Figure 1 - TAX316 Disease Free Survival K-M curve**

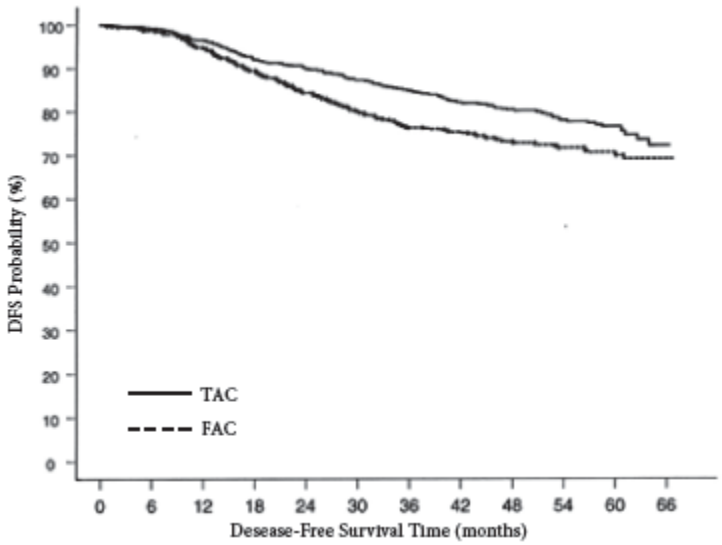
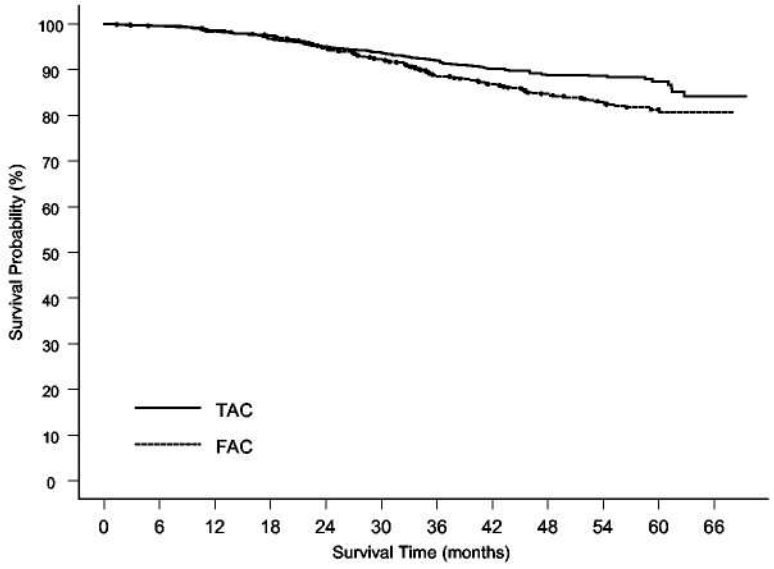


**Figure 2 - TAX316 Overall Survival K-M Curve**




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 | (0.60, 0.92) | 0.69 | (0.53, 0.90) |
| 1-3 | 467 | 0.64 | (0.47, 0.87) | 0.45 | (0.29, 0.70) |
| 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 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-naïve.

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/m$^2$ n=55** | **Best Supportive Care n=49** | **Docetaxel 75 mg/m$^2$ n=125** | **Control (V/I*) n=123** |
| Overall Survival Log-rank | p=0.01 | | p=0.13 | |
| Risk Ratio††, Mortality (Docetaxel: Control) | 0.56 | | 0.82 | |
| 95% CI (Risk Ratio) | (0.35, 0.88) | | (0.63, 1.06) | |
| Median Survival | 7.5 months** | 4.6 months | 5.7 months | 5.6 months |

| | | | | |
|---|---|---|---|---|
| 95% CI | (5.5, 12.8) | (3.7, 6.1) | (5.1, 7.1) | (4.4, 7.9) |
| % 1-year Survival | 37%**† | 12% | 30%**† | 20% |
| 95% CI | (24, 50) | (2, 23) | (22, 39) | (13, 27) |
| Time to Progression | 12.3 weeks** | 7.0 weeks | 8.3 weeks | 7.6 weeks |
| 95% CI | (9.0, 18.3) | (6.0, 9.3) | (7.0,11.7) | (6.7, 10.1) |
| Response Rate | 5.5% | Not Applicable | 5.7% | 0.8% |
| 95% CI | (1.1,15.1) | | (2.3,11.3) | (0.0, 4.5) |

* Vinorelbine/Ifosfamide

** $p \leq 0.05$; †uncorrected for multiple comparisons;†† a value less than 1.00 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**

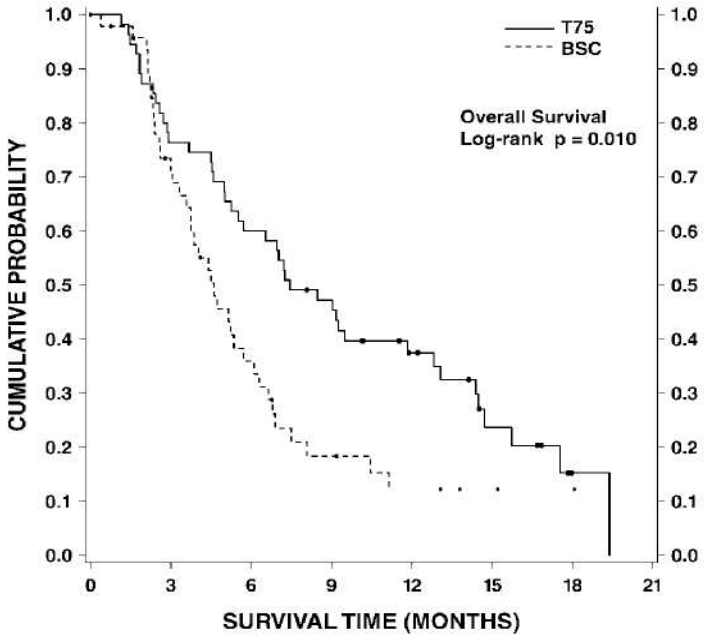
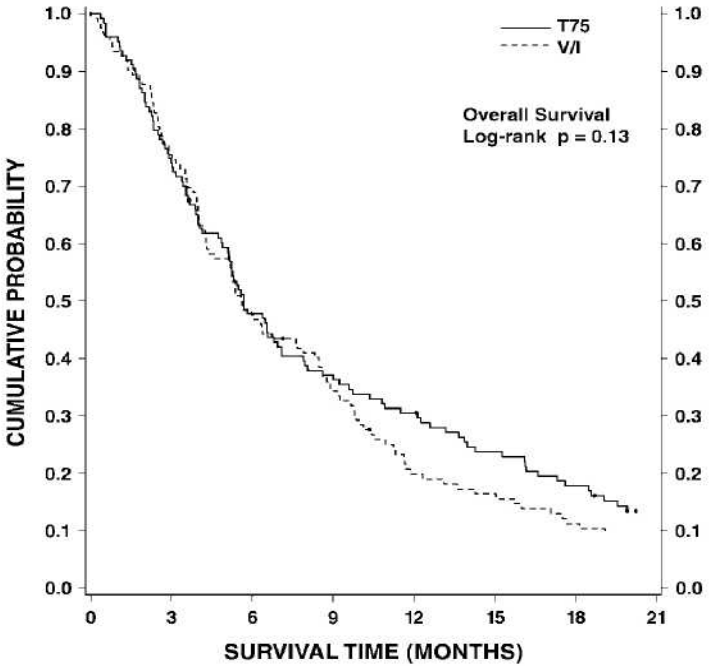


**Figure 4 - TAX320 Survival K-M Curves - Docetaxel 75 mg/m$^2$ vs. Vinorelbine or Ifosfamide Control**




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-Naïve 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 to 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-Naïve 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-Naïve 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 Hormone Refractory Prostate Cancer

The safety and efficacy of docetaxel in combination with prednisone in patients with androgen independent (hormone refractory) metastatic 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.

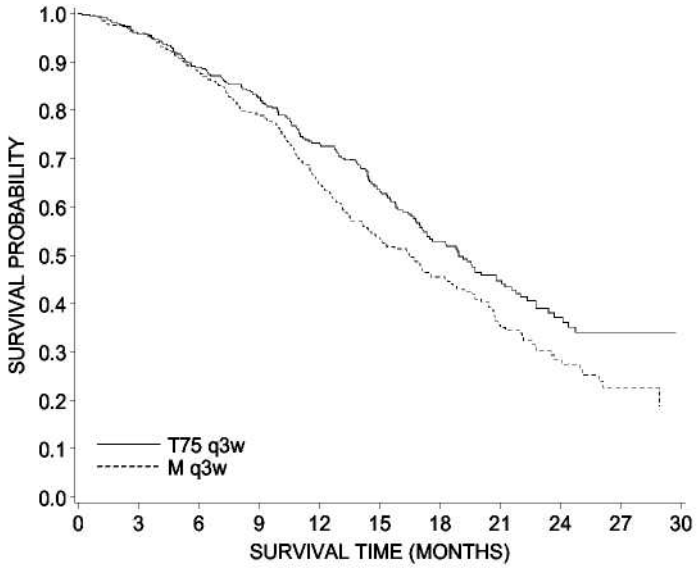
In the docetaxel every three week arm, a statistically significant overall survival advantage was demonstrated compared to mitoxantrone. In the docetaxel weekly arm, no overall survival advantage was demonstrated compared to the mitoxantrone control arm. Efficacy results for the docetaxel every 3 week arm versus the control arm are summarized in **Table 18** and **Figure 5**.

**Table 18 - Efficacy of Docetaxel in the Treatment of Patients with Androgen Independent (Hormone Refractory) Metastatic 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 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 (1000 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 to 1.61). Efficacy results are summarized in **Table 19** and **Figures 6** and **7.**

**Table 19 - Efficacy of Docetaxel in the Treatment of Patients with Gastric Adenocarcinoma**

| **Endpoint** | **TCF n=221** | **CF n=224** |
|---|---|---|
| Median TTP (months) (95% CI) | 5.6 (4.86-5.91) | 3.7 (3.45-4.47) |
| Hazard ratio† (95% CI) *p-value | 0.68 (0.55-0.84) 0.0004 | |
| Median survival (months) (95% CI) | 9.2 (8.38-10.58) | 8.6 (7.16-9.46) |
| Hazard ratio† (95% CI) *p-value | 0.77 (0.62-0.96) 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 1.00 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**

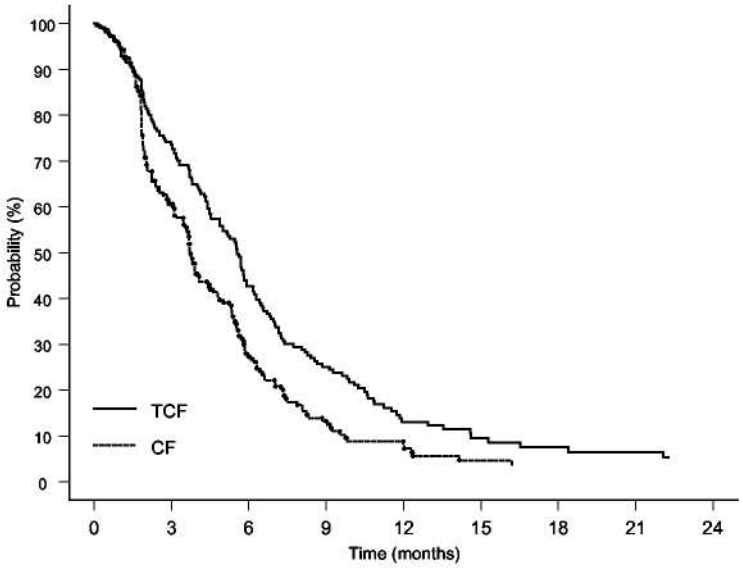
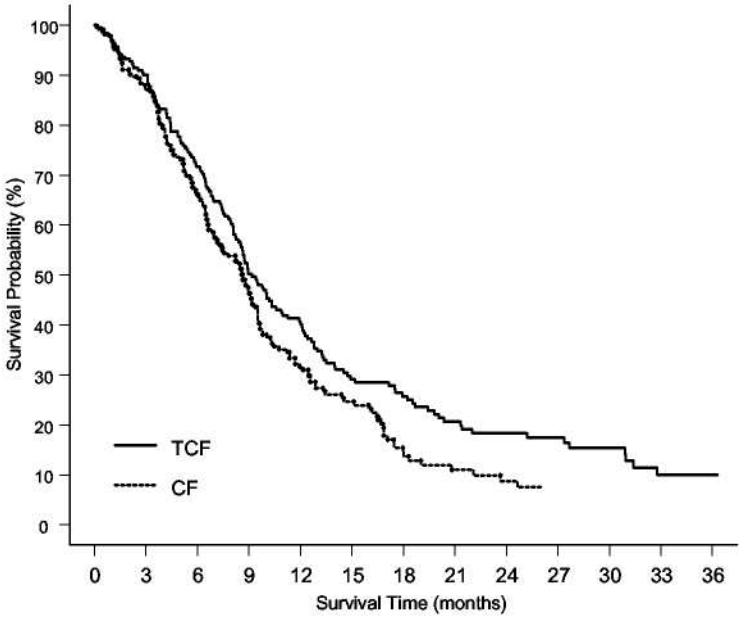



**Figure 7 - Gastric Cancer Study (TAX325) Survival K-M Curve**




### 14.6 Head and Neck Cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of 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) 1000 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)<br>(95% CI) | 11.4<br>(10.1-14.0) | 8.3<br>(7.4-9.1) |
| Adjusted Hazard ratio<br>(95% CI)<br>*p-value | 0.71<br>(0.56-0.91)<br>0.0077 | |
| Median survival (months)<br>(95% CI) | 18.6<br>(15.7-24.0) | 14.2<br>(11.5-18.7) |
| Hazard ratio<br>(95% CI)<br>**p-value | 0.71<br>(0.56-0.90)<br>0.0055 | |
| Best overall response (CR + PR) to chemotherapy (%)<br>(95% CI) | 67.8<br>(60.4-74.6) | 53.6<br>(46.0-61.0) |
| ***p-value | 0.006 | |

| | | |
|---|---|---|
| Best overall response (CR + PR) to study treatment [chemotherapy +/- radiotherapy] (%) (95% CI) | 72.3 (65.1-78.8) | 58.6 (51.0-65.8) |
| ***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**

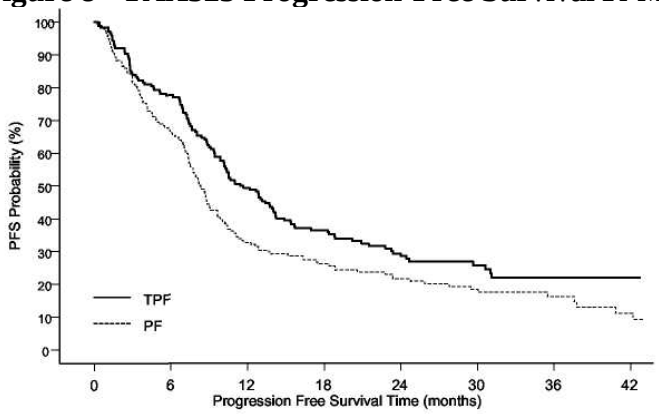
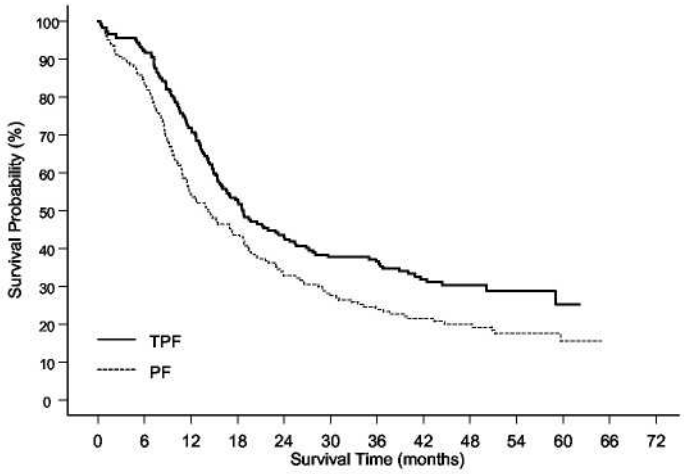



**Figure 9 - TAX323 Overall Survival K-M Curve**




Induction chemotherapy followed by chemoradiotherapy (TAX324)

The safety and efficacy of 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/m$^2$ by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m$^2$ administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m$^2$/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 $mg/m^2$ as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1000 $mg/m^2$/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 anytime following completion of CRT.

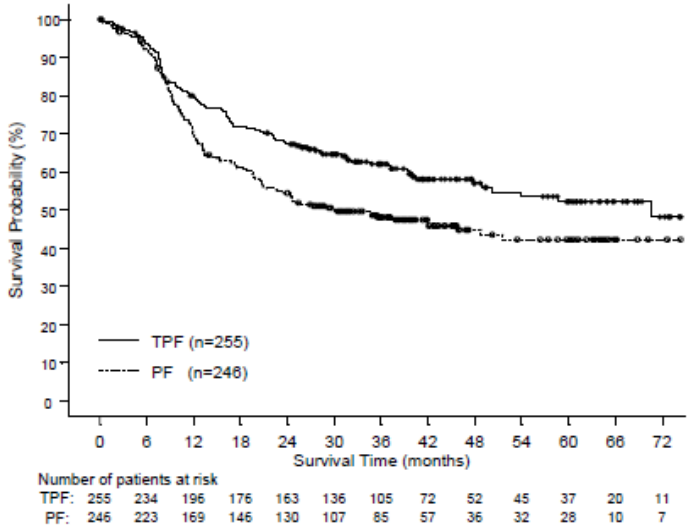
The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, p=0.0058) with the docetaxel-containing regimen compared to PF [median OS: 70.6 versus 30.1 months respectively, hazard ratio (HR)=0.70, 95% confidence interval (CI)= 0.54 to 0.90]. Overall survival results 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)<br>(95% CI) | 70.6<br>(49.0-NE) | 30.1<br>(20.9-51.5) |
| Hazard ratio:<br>(95% CI)<br>*p-value | 0.70<br>(0.54-0.90)<br>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**

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4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy *guidelines and recommendations* for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.


## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Docetaxel Injection is supplied in a multiple dose vial as a sterile, pyrogen-free solution. Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution. The following strengths are available:

| Strength | NDC Number | Volume |
|---|---|---|
| 20 mg/2 mL | 66758-050-01 | Carton of 1 x 2 mL Multiple Dose Vial |
| 80 mg/8 mL | 66758-050-02 | Carton of 1 x 8 mL Multiple Dose Vial |
| 160 mg/16 mL | 66758-050-03 | Carton of 1 x 16 mL Multiple Dose Vial |

### 16.2 Storage

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect

from bright light. Freezing does not adversely affect the product.

After initial puncture, Docetaxel Injection multiple dose vials are stable for 28 days when stored between 2ºC to 8ºC and at room temperature, with or without protection from light.

### 16.3 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

## 17. PATIENT COUNSELING INFORMATION

*See FDA-Approved Patient Labeling*

- Docetaxel Injection may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug. Women of childbearing potential should use effective contraceptives if receiving Docetaxel Injection *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.
- Obtain detailed allergy and concomitant drug information from the patient prior to Docetaxel Injection administration.
- 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.
- Instruct patients to immediately report signs of a hypersensitivity reaction.
- Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea.
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.
- Instruct patients to report myalgia, cutaneous, or neurologic reactions.
- Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, fatigue, excessive tearing, infusion site reactions, and hair loss are associated with docetaxel administration.
- Explain to patients the possible effects of the alcohol content in Docetaxel Injection, including possible effects on the central nervous system. Patients in whom alcohol should be avoided or minimized should consider the alcohol content of Docetaxel Injection. Alcohol could impair their ability to drive or use machines immediately after infusion.

**Patient Information**

Docetaxel (doe-se-TAKS-el) Injection
Intravenous Infusion

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 doctor 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.**

1. **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

2. **Docetaxel Injection can affect your blood cells.** Your doctor 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 doctor may not treat you with Docetaxel Injection until you have enough white blood cells. People with low white blood counts can develop life threatening infections. The earliest sign of infection may be fever. Follow your doctor's instructions for how often to take your temperature while taking Docetaxel Injection. Call your doctor right away if you have a fever.

3. **Serious allergic reactions** can happen in people who take Docetaxel Injection. Serious allergic reactions are medical emergencies that can lead to death and must be treated right away.
   Tell your doctor right away if you have any of these signs of a serious 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.

4. **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 doctor tells you. Tell your doctor or nurse before your Docetaxel Injection treatment if you forget to take the corticosteroid dose or do not take it as your doctor tells you.

**What is Docetaxel Injection?**

**Docetaxel Injection is a prescription anti-cancer medication 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.

**Who should not receive Docetaxel Injection?**
Do not receive Docetaxel Injection if you:

- have had a severe allergic reaction to:
  - docetaxel, the active ingredient in Docetaxel Injection, **or**
  - any other medicines that contain polysorbate 80. Ask your doctor 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.
- have a low white blood cell count.

**What should I tell my doctor before receiving Docetaxel Injection?**

Before you receive Docetaxel Injection, tell your doctor if you:

- are allergic to any medicines. See "Who should not receive Docetaxel Injection?" Also, see the end of this leaflet for a complete list of the ingredients in Docetaxel Injection.
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. Docetaxel Injection can harm your unborn baby. You should not become pregnant during treatment with Docetaxel Injection. Talk to your doctor about effective birth control while receiving Docetaxel Injection.
- are breastfeeding or plan to breastfeed. It is not known if docetaxel passes into your breast milk. You and your doctor should decide if you will receive Docetaxel Injection or breastfeed.

**Tell your doctor 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 doctor 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 doctor will decide how long you will receive treatment with Docetaxel Injection.
- Your doctor 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 doctor 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 take 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.
- **Neurologic Symptoms** including numbness, tingling, or burning in your hands and feet.
- **Vision Problems** including blurred vision or loss of vision**.**
- **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.

The most common side effects of Docetaxel Injection include:

- changes in your sense of taste
- feeling short 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
- rash
- 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 doctor if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of Docetaxel Injection. For more information ask your doctor or pharmacist.

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

**General information about Docetaxel Injection**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This Patient Information leaflet summarizes the most important information about Docetaxel Injection. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Docetaxel Injection that is written for health professionals.

For more information, call 1-800-525-8747.

**What are the ingredients in Docetaxel Injection?**
Active ingredient: docetaxel
Inactive ingredients: alcohol, citric acid, polyethylene glycol 300, and polysorbate 80

**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 doctor 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 doctor tells you.**

***Oral corticosteroid dosing:***

Date:_____ Time:_____

Date:_____ Time:_____
(**Docetaxel Injection Treatment Day)**

Time:_____

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Manufactured by:

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