For the use of an Oncologist or a Hospital or a Laboratory only

DTAXANE

(Docetaxel Injection I.P. Concentrate)

COMPOSITION

DTAXANE 20

Each combi pack contains:

A. 1 vial of Docetaxel Injection I.P. Concentrate

Each single dose vial contains:
Docetaxel Trihydrate I.P. equivalent to
Anhydrous Docetaxel 20 mg
Polysorbate 80 I.P. q.s. to 0.5 ml

B. 1 vial of solvent for Docetaxel Injection I.P. Concentrate

Each vial contains:
Alcohol (95%v/v) I.P. 13% w/v
(Absolute alcohol I.P. contents 15.25% v/v)
Water for injections I.P. q.s. to 1.5 ml

DTAXANE 80

Each combi pack contains:

A. 1 vial of Docetaxel Injection I.P. concentrate

Each single dose vial contains:
Docetaxel Trihydrate I.P. equivalent to
Anhydrous Docetaxel 80 mg
Polysorbate 80 I.P. q.s. to 2.0 ml

B. 1 vial of solvent for Docetaxel Injection I.P. concentrate

Each vial contains:
Alcohol (95%v/v) I.P. 13% w/v
(Absolute alcohol I.P. contents 15.25% v/v)
Water for injections I.P. q.s. to 6.0 ml

DTAXANE 120

Each combi pack contains:

A. 1 vial of Docetaxel Injection I.P. concentrate

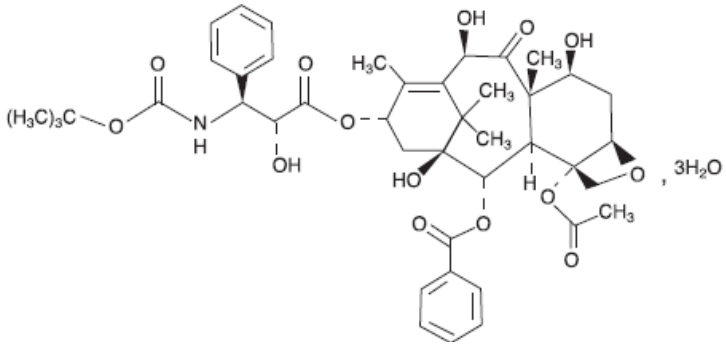
Each single dose vial contains:
Docetaxel Trihydrate I.P. equivalent to
Anhydrous Docetaxel 120 mg
Polysorbate 80 I.P. q.s. to 3.0 ml

B. 1 vial of solvent for Docetaxel Injection I.P. concentrate

Each vial contains:
Alcohol (95%v/v) I.P. 13% w/v
(Absolute alcohol I.P. contents 15.25% v/v)
Water for injections I.P. q.s. to 9.0 ml

DESCRIPTION

Docetaxel is an anti-neoplastic agent belonging to the taxoid family. The chemical name for docetaxel trihydrate is N-debenzoyl-N-(tert-butoxycarbonyl)-10-deacetyltaxol trihydrate. Docetaxel has empirical formula of $C_{43}H_{53}NO_{14}\bullet\ 3H_2O$, and a molecular weight of 861.9. Docetaxel has the following structural formula:



CLINICAL PHARMACOLOGY

Pharmacodynamics

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

Pharmacokinetics

Absorption:

After administration of 20 mg/m^2 to 115 mg/m^2 the area under the curve (AUC) is dose proportional following doses of 70 mg/m2 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 is 21 L/h/m^2.

Distribution:

Doctaxel initially get distributed 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 is 113 L. Docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins.

Metabolism:

Docetaxel gets metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Elimination:
Docetaxel gets eliminated in both the urine and feces following oxidative metabolism of the tertbutyl ester group, but fecal excretion is the main elimination route. About 80% is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

INDICATIONS

Breast Cancer:
Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy and in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node positive breast cancer.

Non-Small Cell Lung Cancer:
Docetaxel as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer:
Docetaxel in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Gastric Adenocarcinoma:
Docetaxel in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.

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

DOSAGE AND ADMINISTRATION RECONSTITUTION:

Reconstitute Docetaxel injection I.P. concentrate after bringing it to room temperature using the solvent for Docetaxel injection I.P. concentrate use 1.5 ml Solvent pack for 20 mg, 6 ml Solvent pack for 80 mg and 9 ml Solvent pack for 120 mg. Rotate the vial gently and allow the premix to stand for 5 minutes. The solution should be clear and homogenous. Use this Docetaxel premix for further dilution.

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Recommended dose
For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used.Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities. For prostate cancer, given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion. Docetaxel is administered as a one-hour infusion every three weeks.

Breast cancer
In the adjuvant treatment of operable node-positive and node negative breast cancer, the recommended dose of docetaxel is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (TAC regimen). For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given incombination therapy with doxorubicin (50 mg/m^2).

In combination with trastuzumab the recommended dose of docetaxel is 100 mg/m^2 every three weeks, with trastuzumab administered weekly. In the pivotal study the initial docetaxel infusion was started the day following the first dose of trastuzumab. The subsequent docetaxel doses were administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. For trastuzumab dose and administration, see trastuzumab summary of product characteristics.In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 twice daily (within 30 minutes after a meal) for 2 weeks followed by a 1 week rest period.

Non-small cell lung cancer
In chemotherapy naïve patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m^2 as a single agent.

Prostate cancer
The recommended dose of docetaxel is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

Gastric adenocarcinoma
The recommended dose of docetaxel is 75 mg/m^2 as a 1-hour infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3-hour infusion (both on day 1 only), followed by 5 fluorouracil 750 mg/m^2 per day given as a 24 hour continuous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of haematological toxicities.

Head and neck cancer
Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

● Induction chemotherapy followed by radiotherapy For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5 fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

● Induction chemotherapy followed by chemoradiotherapy For the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, and aiming at organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3-hour infusion, followed by 5-fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy.

Dose adjustments during treatment
General
Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100 mg/m2 to 75 mg/m^2 and/or from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Adjuvant therapy for breast cancer
Primary G-CSF prophylaxis should be considered in patients who receive docetaxel, doxorubicin and cyclophosphamide (TAC) adjuvant therapy for breast cancer. Patients who experience febrile neutropenia and/or neutropenic infection should have their docetaxel dose reduced to 60 mg/m^2 in all subsequent cycles. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60 mg/m^2.

In combination with cisplatin
For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the docetaxel dose in subsequent cycles should be reduced to 65 mg/m^2.

In combination with capecitabine

● For patients developing the first appearance of Grade 2 toxicity, which persists at the time of the next docetaxel/ capecitabine treatment, delay treatment until resolved to Grade 01, and resume at 100% of the original dose.

● For patients developing the second appearance of Grade 2 toxicity, or the first appearance of Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 01 and then resume treatment with docetaxel 55 mg/m^2.

● For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose

In combination with cisplatin and 5 fluorouracil

If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist . Recommended dose modifications for toxicities in patients treated with docetaxel in combination with cisplatin and 5 fluorouracil (5 FU):

Toxicity	**Dose adjustment**
Diarrhoea grade 3	First episode: reduce 5 FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.
Diarrhoea grade 4	First episode: reduce docetaxel and 5 FU doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce 5 FU dose by 20%. Second episode: stop 5 FU only, at all subsequent cycles. Third episode: reduce docetaxel dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop 5 FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%.

In the pivotal SCCHN studies patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg, day 6-15) in all subsequent cycles.

Special populations

Patients with hepatic impairment

Based on pharmacokinetic data with docetaxel at 100 mg/ m^2 as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2. For those patients with serum bilirubin > ULN and/or ALT and AST > 3.5 times the ULN associated with alkaline phosphatase > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination in the other indications.

Paediatric population
The safety and efficacy of Docetaxel in nasopharyngeal carcinoma in children aged 1 month to less than 18 years have not yet been established.There is no relevant use of Docetaxel in the paediatric population in the indications breast cancer, non-small cell lung cancer, prostate cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma.

Elderly
Based on a population pharmacokinetic analysis, there are no special instructions for use in the elderly. In combination with capecitabine, for patients 60 years of age or more, a starting dose reduction of capecitabine to 75% is recommended.

CONTRAINDICATIONS

- Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.
- Docetaxel should not be used in patients with neutrophil counts of < 1,500 cells/mm^3.
- Patients with severe liver impairment.
- Contraindications for other medicinal products also apply, when combined with docetaxel.

WARNINGS AND PRECAUTIONS

Toxic Deaths

Breast Cancer
Docetaxel administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2 , mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer
Docetaxel administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry.

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

Hematologic Effects
Perform frequent peripheral blood cell counts on all patients receiving Docetaxel. Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3 .
A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel cycle.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of Docetaxel and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils <1500 cells/mm^3

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related.

Three breast cancer patients with severe liver impairment (bilirubin >1.7 times ULN) developed fatal gastrointestinal bleeding associated with severe drug-induced thrombocytopenia. In gastric cancer patients treated with docetaxel in combination with cisplatin and fluorouracil (TCF), febrile neutropenia and/or neutropenic infection occurred in 12% of patients receiving G-CSF compared to 28% who did not. Patients receiving TCF should be closely monitored during the first and subsequent cycles for febrile neutropenia and neutropenic infection.

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

Fluid Retention
Severe fluid retention has been reported following Docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel administration to reduce the incidence and severity of fluid retention**.** Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m^2. Nine of 92 patients (9.8%) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m^2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of Docetaxel to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g*., salt restriction, oral diuretic(s).

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

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

Neurologic Reactions
Severe neurosensory symptoms (*e.g.* paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Eye Disorders
Cystoid macular edema (CME) has been reported in patients treated with Docetaxel. Patients with impaired vision should undergo a prompt and comprehensive ophthalmologic examination. If CME is diagnosed, Docetaxel treatment should be discontinued and appropriate treatment initiated. Alternative non-taxane cancer treatment should be considered.

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

Each administration of Docetaxel Injection at 100 mg/m^2 delivers 1.425 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 2.85 grams of ethanol. Other docetaxel products may have a different amount of alcohol.

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

Use in Pregnancy
Docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.

There are no adequate and well-controlled studies in pregnant women using Docetaxel. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category D
Based on its mechanism of action and findings in animals, Docetaxel can cause fetal harm when administered to a pregnant woman. If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel.

Docetaxel can cause fetal harm when administered to a pregnant woman. Studies in both rats and rabbits at doses ≥0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m^2 basis), administered during the period of organogenesis, have shown that Docetaxel is embryotoxic and fetotoxic (characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

Nursing Mothers
It is not known whether docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Docetaxel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The alcohol content of Docetaxel Injection should be taken into account when given to pediatric patients

The efficacy of Docetaxel in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of Docetaxel in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

Docetaxel has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-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/m²) in combination with cisplatin (75 mg/m²) and 5-fluorouracil (750 mg/m²) (TCF) or to cisplatin (80 mg/m²) and 5-fluorouracil (1000 mg/m²/day) (CF). The primary endpoint was the CR rate following induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response.

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 4.20±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.

The alcohol content of Docetaxel Injection should be taken into account when given to pediatric patients.

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-naïve 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-naïve, 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 , 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 more than 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.

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

The alcohol content of Docetaxel Injection should be taken into account when given to patients with hepatic impairment.

DRUG INTERACTIONS

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel, close monitoring for toxicity and a Docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

ADVERSE REACTIONS

The most serious adverse reactions from docetaxel are:

- Toxic Deaths
- Hepatotoxicity
- Neutropenia
- Hypersensitivity
- Fluid Retention

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia,

dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication. Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Clinical Trial Experience Breast Cancer
Monotherapy with docetaxel for locally advanced or metastatic breast cancer after failure of prior chemotherapy
Docetaxel 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to docetaxel. At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving docetaxel for the treatment of breast cancer and in patients with other tumor types.

Table 3 -Summary of Adverse Reactions in Patients Receiving Docetaxel at 100 mg/m^2

Adverse Reaction	**All Tumor Types Normal LFTs* n=2045 %**	**All Tumor Types Elevated LFTs** n=61 %**	**Breast Cancer Normal LFTs* n=965 %**
Hematologic			
Neutropenia			
<2000 cells/mm^3	96	96	99
<500 cells/mm^3	75	88	86
Leukopenia			
<4000 cells/mm^3	96	98	99
<1000 cells/mm^3	32	47	44
Thrombocytopenia			
<100,000 cells/mm^3	8	25	9
Anemia			
<11 g/dL	90	92	94
<8 g/dL	9	31	8
Febrile Neutropenia***	11	26	12
Septic Death Non-Septic Death	2 1	5 7	1 1
Infections			

Any	22	33	22
Severe	6	16	6
Fever in Absence of Infection			
Any	31	41	35
Severe	2	8	2
Hypersensitivity Reactions			
Regardless of Premedication			
Any	21	20	18
Severe	4	10	3
With 3-day Premedication	n=92	n=3	n=92
Any	15	33	15
Severe	2	0	2
Fluid Retention			
Regardless of Premedication			
Any	47	39	18
Severe	7	8	3
With 3-day Premedication	n=92	n=3	n=92
Any	64	67	15
Severe	7	33	2
Neurosensory			
Any	49	34	58
Severe	4	0	6
Cutaneous			
Any	48	54	47
Severe	5	10	5
Nail Changes			
Any	31	23	41
Severe	3	5	4
Gastrointestinal			
Nausea	39	38	42
Vomiting	22	23	23
Diarrhea	39	33	43
Severe	5	5	6
Stomatitis			
Any	42	49	52
Severe	6	13	7
Alopecia	76	62	74
Asthenia			
Any	62	53	66
Severe	13	25	15

Myalgia			
Any	19	16	21
Severe	2	2	2
Arthralgia	9	7	8
Infusion Site Reactions	4	3	4

***** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.
****** Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.
******* Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization.

Hematologic Reactions
Reversible marrow suppression was the major dose-limiting toxicity of docetaxel. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles.

Febrile neutropenia (<500 cells/mm^3 with fever >38°C with intravenous antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids.

Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions
Severe hypersensitivity reactions have been reported. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and instituting appropriate therapy.

Fluid Retention
Fluid retention can occur with the use of docetaxel.

Cutaneous Reactions
Severe skin toxicity is discussed elsewhere in the label. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after docetaxel infusion, recovered before the next infusion, and were not disabling.

Severe nail disorders were characterized by hypo-or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

Gastrointestinal Reactions
Nausea, vomiting, and diarrhea were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids.

Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

Cardiovascular Reactions
Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. Seven of 86 (8.1%) of metastatic breast cancer patients receiving docetaxel 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with a drop below the institutional lower limit of normal.

Infusion Site Reactions
Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

Hepatic Reactions
In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in AST or ALT >1.5 times the ULN, or alkaline phosphatase >2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on docetaxel, increases in AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. Whether these changes were related to the drug or underlying disease has not been established.

Hematologic and Other Toxicity: Relation to dose and baseline liver chemistry abnormalities
Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given docetaxel at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given docetaxel at 60 mg/m^2 who had normal LFTs.

Table 4 -Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at Docetaxel 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Reaction	Docetaxel 100 mg/m^2		Docetaxel 60 mg/m^2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Neutropenia			
Any <2000 cells/mm^3	98	100	95
Grade 4 <500 cells/mm^3	84	94	75
Thrombocytopenia			
Any <100,000 cells/mm^3	11	44	14
Grade 4 <20,000 cells/mm^3	1	17	1
Anemia <11 g/dL	95	94	65
Infection* **			
Any	23	39	1
Grade 3 and 4	7	33	0
Febrile Neutropenia** By			
Patient	12	33	0
By Course	2	9	0
Septic Death	2	6	1
Non-Septic Death	1	11	0

***** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.

****** Elevated Baseline LFTs: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.

******* Incidence of infection requiring hospitalization and/or intravenous antibiotics was 8.5% (n=62) among the 730 patients with normal LFTs at baseline; 7 patients had concurrent grade 3 neutropenia, and 46 patients had grade 4 neutropenia.

********Febrile Neutropenia: For 100 mg/m^2, ANC grade 4 and fever >38°C with intravenous antibiotics and/or hospitalization; for 60 mg/m^2, ANC grade 3/4 and fever >38.1°C.

Table 5 -Non-Hematologic Adverse Reactions in Breast Cancer Patients Previously Treated with Chemotherapy Treated at Docetaxel 100 mg/m^2 with Normal or Elevated Liver Function Tests or 60 mg/m^2 with Normal Liver Function Tests

Adverse Reaction	Docetaxel 100 mg/m2		Docetaxel 60 mg/m2
	Normal LFTs* n=730 %	Elevated LFTs** n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13	6	1
Severe	1	0	0

Fluid Retention* Regardless of Premedication**			
Any	56	61	13
Severe	8	17	0
Neurosensory			
Any	57	50	20
Severe	6	0	0
Myalgia	23	33	3
Cutaneous			
Any	45	61	31
Severe	5	17	0
Asthenia			
Any	65	44	66
Severe	17	22	0
Diarrhea			
Any	42	28	NA
Severe	6	11	
Stomatitis			
Any	53	67	19
Severe	8	39	1

NA = not available

***** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.

****** Elevated Baseline Liver Function: AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN.

*******Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites); no premedication given with the 60 mg/m^2 dose.

In the three-arm monotherapy trial, TAX313, which compared docetaxel 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with docetaxel 60 mg/m^2 compared to 55.3% and 65.9% treated with 75 mg/m^2 and 100 mg/m^2 respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m vs. 6.9% and 16.5% for patients treated at 75 mg/m^2 and 100 mg/m^2 respectively. Deaths within 30 days of last treatment occurred in 4.0% of patients treated with 60 mg/m compared to 5.3% and 1.6% for patients treated at 75 mg/m^2 and 100 mg/m^2 respectively.

The following adverse reactions were associated with increasing docetaxel doses: fluid retention (26%, 38%, and 46% at 60 mg/m^2, 75 mg/m^2, and 100 mg/m respectively), thrombocytopenia (7%, 11% and 12% respectively), neutropenia (92%, 94%, and 97% respectively), febrile neutropenia (5%, 7%, and 14% respectively), treatment-related grade 3/4 infection (2%, 3%, and 7% respectively) and anemia (87%, 94%, and 97% respectively).

Combination therapy with docetaxel in the adjuvant treatment of breast cancer

The following table presents treatment emergent adverse reactions observed in 744 patients, who were treated with docetaxel 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide.

Table 6 -Clinically Important Treatment Emergent Adverse Reactions Regardless of Causal Relationship in Patients Receiving Docetaxel in Combination with Doxorubicin and Cyclophosphamide.

	Docetaxel 75 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide 500 mg/m2 (TAC) n=744 %		**Fluorouracil 500 mg/m^2+ Doxorubicin 50 mg/m^2+ Cyclophosphamide500 mg/m2 (FAC) n=736 %**	
Adverse Reaction	**Any**	**Grade 3/4**	**Any**	**Grade 3/4**
Anemia	92	4	72	2
Neutropenia	71	66	82	49
Fever in absence of infection	47	1	17	0
Infection	39	4	36	2
Thrombocytopenia	39	2	28	1
Febrile neutropenia	25	N/A	3	N/A
Neutropenic infection	12	N/A	6	N/A
Hypersensitivity reactions	13	1	4	0
Lymphedema	4	0	1	0
Fluid Retention*	35	1	15	0
Peripheral edema	27	0	7	0
Weight gain	13	0	9	0
Neuropathy sensory	26	0	10	0
Neuro-cortical	5	1	6	1
Neuropathy motor	4	0	2	0
Neuro-cerebellar	2	0	2	0
Syncope	2	1	1	0
Alopecia	98	N/A	97	N/A
Skin toxicity	27	1	18	0
Nail disorders	19	0	14	0
Nausea	81	5	88	10
Stomatitis	69	7	53	2
Vomiting	45	4	59	7
Diarrhea	35	4	28	2
Constipation	34	1	32	1
Taste perversion	28	1	15	0
Anorexia	22	2	18	1
Abdominal Pain	11	1	5	0
Amenorrhea	62	N/A	52	N/A
Cough	14	0	10	0
Cardiac dysrhythmias	8	0	6	0

Vasodilatation	27	1	21	1
Hypotension	2	0	1	0
Phlebitis	1	0	1	0
Asthenia	81	11	71	6
Myalgia	27	1	10	0
Arthralgia	19	1	9	0
Lacrimation disorder	11	0	7	0
Conjunctivitis	5	0	7	0

*****COSTART term and grading system for events related to treatment.

Of the 744 patients treated with TAC, 36.3% experienced severe treatment emergent adverse reactions compared to 26.6% of the 736 patients treated with FAC. Dose reductions due to hematologic toxicity occurred in 1% of cycles in the TAC arm versus 0.1% of cycles in the FAC arm. Six percent of patients treated with TAC discontinued treatment due to adverse reactions, compared to 1.1% treated with FAC; fever in the absence of infection and allergy being the most common reasons for withdrawal among TAC-treated patients. Two patients died in each arm within 30 days of their last study treatment; 1 death per arm was attributed to study drugs.

Fever and Infection

Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of TAC-and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in either treatment arm.

Gastrointestinal Reactions

In addition to gastrointestinal reactions reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation vs. one patient in the FAC arm. Five of the 7 TAC-treated patients required treatment discontinuation; no deaths due to these events occurred.

Cardiovascular Reactions

More cardiovascular reactions were reported in the TAC arm vs. the FAC arm; dysrhythmias, all grades (7.9% vs. 6.0%), hypotension, all grades (2.6% vs. 1.1%) and CHF (2.3% vs. 0.9%, at 70 months median follow-up). One patient in each arm died due to heart failure.

Acute Myeloid Leukemia (AML)

Treatment-related acute myeloid leukemia or myelodysplasia is known to occur in patients treated with anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurs at a higher frequency when these agents are given in combination with radiation therapy. AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at 5 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. This risk of AML is comparable to the risk observed for other anthracyclines/cyclophosphamide containing adjuvant breast chemotherapy regimens.

Lung Cancer

Monotherapy with docetaxel for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy

Docetaxel 75 mg/m^2: Treatment emergent adverse drug reactions are shown in Table 7. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or where otherwise noted.

Table 7 -Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving Docetaxel as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy* Adverse Reaction

	Docetaxel 75 mg/m^2 n=176 %	Best Supportive Care n=49 %	Vinorelbine/Ifosfamide n=119 %
Neutropenia			
Any	84	14	83
Grade 3/4	65	12	57
Leukopenia			
Any	84	6	89
Grade 3/4	49	0	43
Thrombocytopenia			
Any	8	0	8
Grade 3/4	3	0	2
Anemia			
Any	91	55	91
Grade 3/4	9	12	14
Febrile Neutropenia**	6	NA†	1
Infection Any Grade	34	29	30
3/4	10	6	9
Treatment Related Mortality	3	NA†	3
Hypersensitivity Reactions			
Any	6	0	1
Grade 3/4	3	0	0
Fluid Retention			
Any	34	ND††	23
Severe	3		3
Neurosensory			
Any	23	14	29
Grade 3/4	2	6	5
Neuromotor	16	8	10

Any Grade 3/4	5	6	3
Skin Any Grade 3/4	 20 1	 6 2	 17 1
Gastrointestinal Nausea Any Grade 3/4	 34 5	 31 4	 31 8
Vomiting Any Grade ¾ Diarrhea Any Grade 3/4	 22 3 23 3	 27 2 6 0	 22 6 12 4
Alopecia	56	35	50
Asthenia Any Severe***	 53 18	 57 39	 54 23
Stomatitis Any Grade 3/4	26 2	6 0	8 1
Pulmonary Any Grade 3/4	 41 21	 49 29	 45 19
Nail Disorder Any Severe***	 11 1	 0 0	 2 0
Myalgia Any Severe***	 6 0	 0 0	 3 0

***** Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN.

****** Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization.

† Not Applicable.

†† Not Done.

*******COSTART term and grading system.

Combination therapy with docetaxel in chemotherapy-naïve advanced unresectable or metastatic NSCLC

Table 8 presents safety data from two arms of an open label, randomized controlled trial that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

Table 8 -Adverse Reactions Regardless of Relationship to Treatment in Chemotherapy-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving Docetaxel in Combination with Cisplatin

	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	47	
Any		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 (2.0%) 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, 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.

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

	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 Injection 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 Injection 75 mg/m^2 in combination with cisplatin and fluorouracil.

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

	Docetaxel Injection 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		**Cisplatin 100 mg/m2 + fluorouracil 1000 mg/m2 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 Injection in Head and Neck Cancer

Table 11 summarizes the safety data obtained from patients that received induction chemotherapy 2 with Docetaxel Injection 75 mg/m 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 Injection in Combination with cisplatin and fluorouracil followed by radiotherapy or chemoradiotherapy

	Docetaxel Injection in Combination with cisplatin and fluorouracil followed by radiotherapy (n=355)				**Docetaxel Injection in Combination with cisplatin and fluorouracil followed by chemoradiotherapy (n=494)**			
	Docetaxel Injection arm (n=174)		**Comparator arm (n=181)**		**Docetaxel Injection 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** Edema only Weight gain only	20 13 6	0 0 0	14 7 6	1 0 0	13 12 0	1 1 0	7 6 1	2 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/dysphagi a/ 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.

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 liver disorders, have been reported.

Neurologic
Confusion, rare cases of seizures or transient loss of consciousness have been observed, sometimes appearing during the infusion of the drug.

Ophthalmologic
Conjunctivitis, lacrimation or lacrimation with or without conjunctivitis. Excessive tearing which may be attributable to lacrimal duct obstruction has been reported. Rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.

Hearing
Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Respiratory
Dyspnea, acute pulmonary edema, acute respiratory distress syndrome/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
Cases of hyponatremia have been reported.

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, USP and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection, USP close monitoring for toxicity and a Docetaxel Injection, USP dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

OVERDOSAGE

There is no known antidote for docetaxel overdosage. In case of overdosage, the patient should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident. In mice, lethality was observed following single intravenous doses that were 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.

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WARNING

Solvent for Docetaxel injection I.P. concentrate to be used as diluent and not to be injected as such

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store between 2^{o}C & 8^{o}C. Protected from light and moisture. Do not freeze.
Keep out of reach of children

PRESENTATION
DTAXANE 20 is available as combipack containing single dose vial of Docetaxel Injection I.P. concentrate of 20 mg with solvent of Docetaxel Injection I.P. 1.5 ml.

DTAXANE 80 is available as combipack containing single dose vial of Docetaxel Injection I.P. concentrate of 80 mg with solvent of Docetaxel Injection I.P. 6.0 ml.

DTAXANE 120 is available as combipack containing single dose vial of Docetaxel Injection I.P. concentrate of 120 mg with solvent of Docetaxel Injection I.P. 9.0 ml.

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