FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Treatment-related mortality associated with docetaxel is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m^2 *[see Warnings and Precautions (5.1)]*.

Avoid the use of Docetaxel Injection in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia. Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of Docetaxel Injection *[see Warnings and Precautions (5.2)]*.

Do not administer Docetaxel Injection to patients with neutrophil counts of <1500 cells/mm^3. Monitor blood counts frequently as neutropenia may be severe and result in infection *[see Warnings and Precautions (5.3)]*.

Do not administer Docetaxel Injection to patients who have a history of severe hypersensitivity reactions to Docetaxel Injection or to other drugs formulated with polysorbate 80 *[see Contraindications (4)]*. Severe hypersensitivity reactions have been reported in patients despite dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and administration of appropriate therapy *[see Warnings and Precautions (5.5)]*.

- For the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel Injection dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 courses. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities *[see Dosage and Administration (2.7)]*.

2.2 Non-Small Cell Lung Cancer

- For treatment after failure of prior platinum-based chemotherapy, docetaxel was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m^2 in patients previously treated with chemotherapy was associated with increased hematologic toxicity, infection, and treatment-related mortality in randomized, controlled trials *[see Boxed Warning, Dosage and Administration (2.7), Warnings and Precautions (5), Clinical Studies (14)]*.

- For chemotherapy-naive patients, docetaxel was evaluated in combination with cisplatin. The recommended dose of Docetaxel Injection is 75 mg/m^2 administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes every 3 weeks *[see Dosage and Administration (2.7)]*.

2.3 Prostate Cancer

For metastatic castration-resistant prostate cancer, the recommended dose of Docetaxel Injection is 75 mg/m^2 every 3 weeks as a 1 hour intravenous infusion. Prednisone 5 mg orally twice daily is administered continuously *[see Dosage and Administration (2.7)]*.

2.4 Gastric Adenocarcinoma

For gastric adenocarcinoma, the recommended dose of Docetaxel Injection is 75 mg/m^2 as a 1-hour intravenous infusion, followed by cisplatin 75 mg/m^2, as a 1- to 3- hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m^2 per day given as a 24-hour continuous intravenous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration *[see Dosage and Administration (2.7)]*.

2.5 Head and Neck Cancer

Patients must receive premedication with antiemetics, and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. All patients treated on the docetaxel injection containing arms of the TAX323 and TAX324 studies received prophylactic antibiotics.

Induction Chemotherapy Followed by Radiotherapy (TAX323)

For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of Docetaxel Injection is 75 mg/m^2 as a 1-hour intravenous infusion followed by cisplatin 75 mg/m^2 intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy *[see Dosage and Administration (2.7)]*.

Induction Chemotherapy Followed by Chemoradiotherapy (TAX324)

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of Docetaxel Injection is 75 mg/m^2 as a 1-hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy *[see Dosage and Administration (2.7)]*.

2.6 Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to Docetaxel Injection administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.5)]*.

For metastatic castration-resistant prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the Docetaxel Injection infusion *[see Warnings and Precautions (5.5)]*.

2.7 Dosage Adjustments During Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, or severe or cumulative cutaneous reactions during Docetaxel Injection therapy should have the dosage adjusted from 100 mg/m^2 to 75 mg/m^2. If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2 or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m^2 and who do not experience febrile neutropenia, neutrophils <500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or severe peripheral neuropathy during Docetaxel Injection therapy may tolerate higher doses. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination Therapy with Docetaxel Injection in the Adjuvant Treatment of Breast Cancer

Docetaxel Injection in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is ≥1,500 cells/mm^3. Patients who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel Injection dose reduced to 60 mg/ m^2. Patients who experience grade 3 or 4 stomatitis should have their Docetaxel Injection dose decreased to 60 mg/ m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel Injection therapy should have their dosage of Docetaxel Injection reduced from 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/ m^2, treatment should be discontinued.

Non-Small Cell Lung Cancer

Monotherapy with Docetaxel Injection for NSCLC treatment after failure of prior platinum-based chemotherapy

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during Docetaxel Injection treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination therapy with Docetaxel Injection for chemotherapy-naive NSCLC

If a dose greater than 200 mg of Docetaxel Injection is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL Docetaxel Injection is not exceeded.

Thoroughly mix the infusion bag or bottle manually by gentle inversion and rotation in a controlled manner and avoid foaming. Shaking or vigorous agitation should be avoided during preparation and transportation to the patient for administration.

As with all parenteral products, Docetaxel Injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection vial or diluted solution is not clear or appears to have precipitation, these should be discarded.

The Docetaxel Injection diluted solution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature below 25°C (77°F) and lighting conditions.

2.10 Stability

Docetaxel Injection infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours in either 0.9% Sodium Chloride solution or 5% Dextrose solution. Use within 4 hours including storage and administration. Do not freeze infusion solution.

3. DOSAGE FORMS AND STRENGTHS

- 20 mg/2 mL multiple-dose vial
- 80 mg/8 mL multiple-dose vial
- 160 mg/16 mL multiple-dose vial

4. CONTRAINDICATIONS

Docetaxel Injection is contraindicated in patients with:

- neutrophil counts of <1500 cells/mm^3 *[see Warnings and Precautions (5.3)]*.
- a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred *[see Warnings and Precautions (5.5)]*.

5. WARNINGS AND PRECAUTIONS

5.1 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 *[see Dosage and Administration (2.2), Clinical Studies (14)]*.

5.2 Hepatic Impairment

Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death.

Avoid docetaxel in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN *[see Warnings and Precautions (5.1)]*.

For patients with isolated elevations of transaminase >1.5 x ULN, consider docetaxel dose modifications *[see Dosage and Administration (2.7)]*.

Measure bilirubin, AST or ALT, and alkaline phosphatase prior to each cycle of docetaxel therapy.

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving Docetaxel Injection. Do not retreat patients with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1500 cells/mm^3 *[see Contraindications (4)]*. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3.

A 25% reduction in the dose of Docetaxel Injection 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 Injection cycle *[see Dosage and Administration (2.7)]*.

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 Injection 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 *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

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 *[see Dosage and Administration (2.7) Adverse Reactions (6)]*.

5.4 Enterocolitis and neutropenic Colitis

Enterocolitis and neutropenic colitis (typhlitis) have occurred in patients treated with docetaxel alone and in combination with other chemotherapeutic agents, despite the coadministration of G-CSF. Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity *[see Dosage and Administration (2), Warnings and Precautions (5.3), Adverse Reactions (6.2)]*.

5.5 Hypersensitivity Reactions

Monitor patients closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and aggressive therapy. Do not rechallenge patients with a history of severe hypersensitivity reactions with Docetaxel Injection [*see Contraindications (4)]*.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a hypersensitivity reaction to docetaxel that may include severe or fatal reactions such as anaphylaxis. Monitor patients with a previous history of hypersensitivity to paclitaxel closely during initiation of docetaxel therapy.

Hypersensitivity reactions may occur within a few minutes following initiation of a Docetaxel Injection 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 Injection *[see Dosage and Administration (2.6)]*.

5.6 Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each Docetaxel Injection administration to reduce the incidence and severity of fluid retention *[see Dosage and Administration (2.6)]*. 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).

5.7 Second Primary Malignancies

Second primary malignancies, notably acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), Non-Hodgkin's Lymphoma (NHL), and renal cancer, have been reported in patients treated with docetaxel-containing regimens. These adverse reactions may occur several months or years after docetaxel-containing therapy.

Treatment-related AML or MDS 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 *[see Clinical Studies (14.2)]*. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies *[see Adverse Reactions (6.1)]*.

5.8 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 *[see Dosage and Administration (2.7)]*. 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.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Permanent treatment discontinuation should be considered in patients who experience SCARs.

5.9 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 *[see Dosage and Administration (2.7)]*. 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).

5.10 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.

5.11 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.

5.12 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, docetaxel can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of

major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating docetaxel. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of Docetaxel Injection. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of Docetaxel Injection *[see Use in Specific Populations (8.1, 8.3)]*.

5.13 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 2.65 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 5.3 grams of ethanol [*see Description (11)*]. Other docetaxel products may have a different amount of alcohol.

5.14 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with docetaxel *[see Adverse Reactions (6.2)]*. Patients at risk of tumor lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumor) should be closely monitored prior to initiating Docetaxel Injection and periodically during treatment. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

6. ADVERSE REACTIONS

The most serious adverse reactions from docetaxel are:

- Toxic Deaths *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hepatic Impairment *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Hematologic Effects *[see Boxed Warning, Warnings and Precautions (5.3)]*
- Enterocolitis and Neutropenic Colitis *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see- Boxed Warning, Warnings and Precautions (5.5)]*
- Fluid Retention *[see- Boxed Warning, Warnings and Precautions (5.6)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.7)]*
- Cutaneous Reactions *[see Warnings and Precautions (5.8)]*
- Neurologic Reactions *[see Warnings and Precautions (5.9)]*
- Eye Disorders *[see Warnings and Precautions (5.10)]*
- Asthenia *[see Warnings and Precautions (5.11)]*
- Alcohol Content *[see Warnings and Precautions (5.13)]*

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.

6.1 Clinical Trials 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 (see Table 3**)**.

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

Adverse Reaction	**All Tumor Types Normal LFTs[1] n=2045 %**	**All Tumor Types Elevated LFTs[2] n=61 %**	**Breast Cancer Normal LFTs[1] 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[3]	11	26	12
Septic Death	2	5	1
Non-Septic Death	1	7	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

Any	11	0	2
Severe[3]	1	0	0
Myalgia			
Any	6	0	3
Severe[3]	0	0	0
Arthralgia			
Any	3	2	2
Severe[3]	0	0	1
Taste Perversion			
Any	6	0	0
Severe[3]	1	0	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.

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

3. COSTART term and grading system.

4. Not Applicable

5. Not Done

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

Table 8 presents safety data from two arms of an open label, randomized controlled trial (TAX326) 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-Naive Advanced Non-Small Cell Lung Cancer Patients Receiving Docetaxel in Combination with Cisplatin

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[1]		
Any	12	4
Grade 3/4	3	<1
Fluid Retention[2]		
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[2]		
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[2]		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder[2]		
Any	14	<1
All severe events	<1	0
Myalgia[2]		
Any	18	12
All severe events	<1	<1

[1.] Replaces NCI term "Allergy"

[2] 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[1]	24	1	5	0
Weight Gain[1]	8	0	3	0
Peripheral Edema[1]	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

[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 (see Table 10).

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/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[1]	15	0	4	0
Edema[1]	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.

[1.] 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 with docetaxel injection 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 Injection in Combination with Cisplatin and Fluorouracil Followed by Radiotherapy (TAX323) or Chemoradiotherapy (TAX324)

	TAX323 (n=355)				**TAX324 (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[1]	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[2]	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]	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.

1. Febrile neutropenia: grade ≥2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
2. Related to treatment.
3. Includes superficial and deep vein thrombosis and pulmonary embolism.

6.2 Postmarketing Experience

The following adverse reactions have been identified from clinical trials and/or postmarketing surveillance. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole: diffuse pain, chest pain, radiation recall phenomenon, injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) at the site of previous extravasation.

Cardiovascular: atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction. Ventricular arrhythmia, including ventricular tachycardia, in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide, may be associated with fatal outcome.

Cutaneous: cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis, scleroderma-like changes (usually preceded by peripheral lymphedema), severe palmar-plantar erythrodysesthesia and permanent alopecia.

Gastrointestinal: enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, which may be fatal. Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, intestinal obstruction, ileus, and dehydration as a consequence of gastrointestinal events.

Hearing: ototoxicity, hearing disorders and/or hearing loss, including during use with other ototoxic drugs.

Hematologic: bleeding episodes, disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure.

Hepatic: hepatitis, sometimes fatal, primarily in patients with pre-existing liver disorders.

Hypersensitivity: anaphylactic shock with fatal outcome in patients who received premedication. Severe hypersensitivity reactions with fatal outcome with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and Nutrition Disorders: electrolyte imbalance, including hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia. Tumor lysis syndrome, sometimes fatal.

Neurologic: confusion, seizures or transient loss of consciousness, sometimes appearing during the infusion of the drug.

Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis, cystoid macular edema (CME). Excessive tearing which may be attributable to lacrimal duct obstruction. Transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during drug infusion and reversible upon discontinuation of the infusion, in association with hypersensitivity reactions.

Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis, which may be fatal. Radiation pneumonitis in patients receiving concomitant radiotherapy.

Renal: renal insufficiency and renal failure, the majority of cases were associated with concomitant nephrotoxic drugs.

Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer *[see Warnings and Precautions (5.7)]*.

Musculoskeletal disorder: myositis.

7. DRUG INTERACTIONS

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

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection close monitoring for toxicity and a Docetaxel Injection dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action, Docetaxel Injection can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Available data from case reports in the

literature and pharmacovigilance with docetaxel use in pregnant women are not sufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Docetaxel Injection contains alcohol which can interfere with neurobehavioral development *[see Clinical Considerations]*. In animal reproductive studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused an increased incidence of embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively *[see Data]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Docetaxel Injection contains alcohol *[see Warnings and Precautions (5.13)]*. Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Data

Animal data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of docetaxel in human milk, or on its effects on milk production or the breastfed child. No lactation studies in animals have been conducted. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with Docetaxel Injection and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Docetaxel Injection.

Contraception

Females

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

Males

Head and Neck Cancer

Among the 174 and 251 patients who received the induction treatment with docetaxel injection 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 injection in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

8.6 Hepatic Impairment

Avoid docetaxel in patients with bilirubin >ULN and patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN *[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 (5.13)]*.

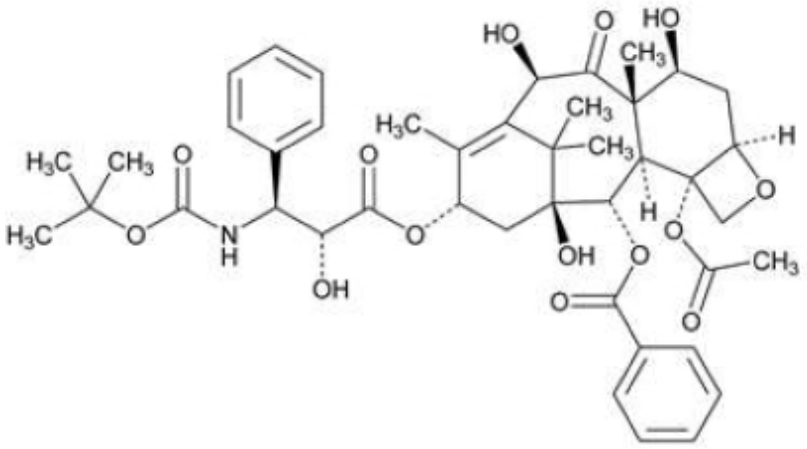
10. OVERDOSAGE

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 Pharmacokinetics

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

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. *In vitro* studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: *In vitro* drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4 *[see Drug Interactions (7)]*.

cyclophosphamide (500 mg/m^2) when administered in combination. The co-administration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to co-administration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed.

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

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

14. CLINICAL STUDIES

14.1 Locally Advanced or Metastatic Breast Cancer

The efficacy and safety of 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[1], Mortality (Docetaxel: Control)	0.73		

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[1]**	**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-naive.

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

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

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

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

17. PATIENT COUNSELING INFORMATION

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

Bone Marrow Suppression

Advise patients that periodic assessment of their blood count will be performed to detect neutropenia, thrombocytopenia, and/ or anemia *[see Contraindications (4), Warnings and Precautions (5.3)]*. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.

Enterocolitis and Neutropenic Colitis

Advise patients of the symptoms of colitis, such as abdominal pain or tenderness, and/or diarrhea, with or without fever, and instruct patients to promptly contact their healthcare provider if they experience these symptoms *[see Dosage and Administration (2.7) and Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Ask patients whether they have previously received paclitaxel therapy, and if they have experienced a hypersensitivity reaction to paclitaxel. Instruct patients to immediately report to their healthcare provider signs of a hypersensitivity reaction *[see Contraindications (4), Warnings and Precautions (5.5)]*.

Fluid Retention

Advise patients to report signs of fluid retention such as peripheral edema in the lower extremities, weight gain, and dyspnea immediately to their healthcare provider *[see Warnings and Precautions (5.6)]*.

Second Primary Malignancies

Advise patients on the risk of second primary malignancies during treatment with docetaxel *[see Warnings and Precautions (5.7)]*.

Cutaneous Reactions

Advise patients that localized erythema of the extremities and severe skin toxicities may occur. Instruct patients to immediately report severe cutaneous reactions to their healthcare provider *[see Dosage and Administration (2.7) and Warnings and Precautions (5.8)]*.

Neurologic Reactions

Advise patients that neurosensory symptoms or peripheral neuropathy may occur. Instruct patients to immediately report neurologic reactions to their healthcare provider *[see Dosage and Administration (2.7) and Warnings and Precautions (5.9)]*.

Eye Disorders

Advise patients that vision disturbances and excessive tearing are associated with Docetaxel Injection administration. Instruct patients to immediately report any vision changes to their healthcare provider *[see Warnings and Precautions (5.10)]*.

Gastrointestinal Reactions

Explain to patients that Docetaxel Injection may impair their ability to drive or operate machines due to its side effects *[see Adverse Reactions (6)]* or due to the alcohol content of Docetaxel Injection *[see Warnings and Precautions (5.13)]*. Advise them not to drive or use machines if they experience these side effects during treatment.

Drug Interactions

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

Manufactured for:

Sandoz Inc.
Princeton, NJ 08540

Manufactured by:

EBEWE Pharma Ges.m.b.H. Nfg.KG
A-4866 Unterach, Austria