

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **DOCETAXEL INJECTION** safely and effectively. See full prescribing information for **DOCETAXEL INJECTION**.

DOCETAXEL INJECTION, for intravenous use

Initial U.S. Approval: 1996

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

See full prescribing information for complete boxed warning

- Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m² (5.1)
- Should not be given if bilirubin > ULN, or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. LFT elevations increase risk of severe or life-threatening complications. Obtain LFTs before each treatment cycle (8.6)
- Should not be given if neutrophil counts are < 1500 cells/mm³. Obtain frequent blood counts to monitor for neutropenia (4)
- Severe hypersensitivity, including very rare fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of Docetaxel Injection and administration of appropriate therapy (5.4)
- Contraindicated if history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80 (4)
- Severe fluid retention may occur despite dexamethasone (5.5)

INDICATIONS AND USAGE

Docetaxel Injection is a microtubule inhibitor indicated for:

- **Breast Cancer (BC):** single agent for locally advanced or metastatic BC after chemotherapy failure; and with doxorubicin and cyclophosphamide as adjuvant treatment of operable node-positive BC (1.1)
- **Non-Small Cell Lung Cancer (NSCLC):** single agent for locally advanced or metastatic NSCLC after platinum therapy failure; and with cisplatin for unresectable, locally advanced or metastatic untreated NSCLC (1.2)
- **Hormone Refractory Prostate Cancer (HRPC):** with prednisone in androgen independent (hormone refractory) metastatic prostate cancer (1.3)
- **Gastric Adenocarcinoma (GC):** with cisplatin and fluorouracil for untreated, advanced GC, including the gastroesophageal junction (1.4)
- **Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN):** with cisplatin and fluorouracil for induction treatment of locally advanced SCCHN (1.5)

DOSAGE AND ADMINISTRATION

Administer in a facility equipped to manage possible complications (e.g., anaphylaxis). Administer intravenously (IV) over 1 hr every 3 weeks. PVC equipment is not recommended. Use only a 21 gauge needle to withdraw Docetaxel Injection from the vial.

- BC locally advanced or metastatic: 60 mg/m² to 100 mg/m² single agent (2.1)
- BC adjuvant: 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles (2.1)
- NSCLC: after platinum therapy failure: 75 mg/m² single agent (2.2)
- NSCLC: chemotherapy-naïve: 75 mg/m² followed by cisplatin 75 mg/m² (2.2)
- HRPC: 75 mg/m² with 5 mg prednisone twice a day continuously (2.3)
- GC: 75 mg/m² followed by cisplatin 75 mg/m² (both on day 1 only) followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion (2.4)

- SCCHN: 75 mg/m² followed by cisplatin 75 mg/m² IV (day 1), followed by fluorouracil 750 mg/m² per day as a 24-hr IV (days 1-5), starting at end of cisplatin infusion; for 4 cycles (2.5)
- SCCHN: 75 mg/m² followed by cisplatin 100 mg/m² IV (day 1), followed by fluorouracil 1000 mg/m² per day as a 24-hr IV (days 1-4); for 3 cycles (2.5)

For all patients:

- Premedicate with oral corticosteroids (2.6)
- Adjust dose as needed (2.7)

DOSAGE FORMS AND STRENGTHS

- 20 mg/2 mL single use vial (3)
- 80 mg/8 mL multi-use vial (3)
- 160 mg/16 mL multi-use vial (3)

CONTRAINDICATIONS

- Hypersensitivity to docetaxel or polysorbate 80 (4)
- Neutrophil counts of <1500 cells/mm³ (4)

WARNINGS AND PRECAUTIONS

- Acute myeloid leukemia: In patients who received docetaxel doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia (5.6)
- Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment (5.7)
- Neurologic reactions: Reactions including paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent (5.8)
- Eye disorders: Cystoid macular edema (CME) has been reported and requires treatment discontinuation (5.9)
- Asthenia: Severe asthenia may occur and may require treatment discontinuation (5.10)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving Docetaxel Injection (5.11, 8.1)
- Alcohol content: The alcohol content in a dose of Docetaxel Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion (5.12)

ADVERSE REACTIONS

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, myalgia (6)

To report **SUSPECTED ADVERSE REACTIONS**, contact Hospira, Inc. at 1-800-441-4100 or electronically at ProductComplaintsPP@hospira.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cytochrome P450 3A4 inducers, inhibitors, or substrates: May alter docetaxel metabolism (7)

See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**.

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FULL PRESCRIBING INFORMATION

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

The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m² [see *Warnings and Precautions* (5.1)].

Docetaxel Injection should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 x ULN concomitant with alkaline phosphatase >2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel Injection therapy [see *Warnings and Precautions* (5.2)].

Docetaxel Injection therapy should not be given to patients with neutrophil counts of <1500 cells/mm³. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving Docetaxel Injection [see *Warnings and Precautions* (5.3)].

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel Injection infusion and administration of appropriate therapy [see *Warnings and Precautions* (5.4)]. Docetaxel Injection must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 [see *Contraindications* (4)].

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) [see *Warnings and Precautions* (5.5)].

1 INDICATIONS AND USAGE

1.1 Breast Cancer

Docetaxel Injection is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

Docetaxel Injection in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

1.2 Non-Small Cell Lung Cancer

Docetaxel Injection 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 Injection 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.

1.3 Prostate Cancer

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

1.4 Gastric Adenocarcinoma

Docetaxel Injection 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.

1.5 Head and Neck Cancer

Docetaxel Injection 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).

2 DOSAGE AND ADMINISTRATION

For all indications, toxicities may warrant dosage adjustments [*see Dosage and Administration (2.7)*].

Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

2.1 Breast Cancer

For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of Docetaxel Injection is 60 mg/m² to 100 mg/m² administered intravenously over 1 hour every 3 weeks.

For the adjuvant treatment of operable node-positive breast cancer, the recommended Docetaxel Injection dose is 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² 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/m² administered intravenously over 1 hour every 3 weeks. A dose of 100 mg/m² 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-naïve patients, docetaxel was evaluated in combination with cisplatin. The recommended dose of Docetaxel Injection is 75 mg/m² administered intravenously over 1 hour immediately followed by cisplatin 75 mg/m² over 30–60 minutes every 3 weeks [*see Dosage and Administration (2.7)*].

2.3 Prostate Cancer

For hormone-refractory metastatic prostate cancer, the recommended dose of Docetaxel Injection is 75 mg/m² 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/m² as a 1 hour intravenous infusion, followed by cisplatin 75 mg/m², as a 1 to 3 hour intravenous infusion (both on day 1 only), followed by fluorouracil 750 mg/m² 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/m² as a 1 hour intravenous infusion followed by cisplatin 75 mg/m² intravenously over 1 hour, on day one, followed by fluorouracil as a continuous intravenous infusion at 750 mg/m² 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/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m² administered as a 30-minute to 3 hour infusion, followed by fluorouracil 1000 mg/m²/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 (5.4)*].

For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the Docetaxel Injection infusion [*see Warnings and Precautions (5.4)*].

2.7 Dosage Adjustments During Treatment

Breast Cancer

Patients who are dosed initially at 100 mg/m² and who experience either febrile neutropenia, neutrophils <500 cells/mm³ for more than 1 week, or severe or cumulative cutaneous reactions during Docetaxel Injection therapy should have the dosage adjusted from 100 mg/m² to 75 mg/m². If the patient continues to experience these reactions, the dosage should either be decreased from 75 mg/m² to 55 mg/m² or the treatment should be discontinued. Conversely, patients who are dosed initially at 60 mg/m² and who do not experience febrile neutropenia, neutrophils <500 cells/mm³ 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/mm³. 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/m². Patients who experience grade 3 or 4 stomatitis should have their Docetaxel Injection dose decreased to 60 mg/m². 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/m² to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², 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/m² and who experience either febrile neutropenia, neutrophils <500 cells/mm³ 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/m². Patients who develop ≥grade 3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Combination therapy with Docetaxel Injection for chemotherapy-naïve NSCLC

For patients who are dosed initially at Docetaxel Injection 75 mg/m² in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm³, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the Docetaxel Injection dosage in subsequent cycles should be reduced to 65 mg/m². In patients who require a further dose reduction, a dose of 50 mg/m² is recommended. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with Docetaxel Injection for hormone-refractory metastatic prostate cancer

Docetaxel Injection should be administered when the neutrophil count is ≥1,500 cells/mm³. Patients who experience either febrile neutropenia, neutrophils <500 cells/mm³ for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during Docetaxel Injection therapy should have the dosage of Docetaxel Injection reduced from 75 mg to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Gastric or Head and Neck Cancer

Docetaxel Injection in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer

Patients treated with Docetaxel Injection in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In both studies, G-CSF was recommended during the second and/or subsequent cycles in case of febrile neutropenia, or documented infection with neutropenia, or neutropenia lasting more than 7 days. If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the Docetaxel Injection dose should be reduced from 75 mg/m² to 60 mg/m². If subsequent episodes of complicated neutropenia occur the Docetaxel Injection dose should be reduced from 60 mg/m² to 45 mg/m². In case of grade 4 thrombocytopenia the Docetaxel Injection dose should be reduced from 75 mg/m² to 60 mg/m². Patients should not be retreated with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. Discontinue treatment if these toxicities persist [see *Warnings and Precautions* (5.3)].

Recommended dose modifications for toxicities in patients treated with Docetaxel Injection in combination with cisplatin and fluorouracil are shown in Table 1.

Table 1 - Recommended Dose Modifications for Toxicities in Patients Treated with Docetaxel Injection in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage Adjustment
Diarrhea grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: then reduce Docetaxel Injection dose by 20%.
Diarrhea grade 4	First episode: reduce Docetaxel Injection and fluorouracil doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: stop fluorouracil only, at all subsequent cycles. Third episode: reduce Docetaxel Injection dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop fluorouracil only, at all subsequent cycles. Second episode: reduce Docetaxel Injection dose by 20%.

Liver dysfunction: In case of AST/ALT >2.5 to ≤5 x ULN and AP ≤2.5 x ULN, or AST/ALT >1.5 to ≤5 x ULN and AP >2.5 to ≤5 x ULN, Docetaxel Injection should be reduced by 20%.

In case of AST/ALT >5 x ULN and/or AP >5 x ULN Docetaxel Injection should be stopped. The dose modifications for cisplatin and fluorouracil in the gastric cancer study are provided below:

Cisplatin dose modifications and delays

Peripheral neuropathy

A neurological examination should be performed before entry into the study, and then at least every 2 cycles and at the end of treatment. In the case of neurological signs or symptoms, more frequent examinations should be performed and the following dose modifications can be made according to NCIC-CTC grade:

- Grade 2: Reduce cisplatin dose by 20%.
- Grade 3: Discontinue treatment.
- Ototoxicity: In the case of grade 3 toxicity, discontinue treatment.

Nephrotoxicity

In the event of a rise in serum creatinine ≥grade 2 (>1.5 x normal value) despite adequate rehydration, CrCl should be determined before each subsequent cycle and the following dose reductions should be considered (see Table 2).

For other cisplatin dosage adjustments, also refer to the manufacturers' prescribing information.

Table 2 – Dose Reductions for Evaluation of Creatinine Clearance

Creatinine Clearance Result Before Next Cycle	Cisplatin Dose Next Cycle
CrCl ≥60 mL/min	Full dose of cisplatin was given. CrCl was to be repeated before each treatment cycle.
CrCl between 40 and 59 mL/min	Dose of cisplatin was reduced by 50% at subsequent cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was reinstated at the next cycle. If no recovery was observed, then cisplatin was omitted from the next treatment cycle.
CrCl <40 mL/min	Dose of cisplatin was omitted in that treatment cycle only. If CrCl was still <40 mL/min at the end of cycle, cisplatin was discontinued. If CrCl was >40 and <60 mL/min at end of cycle, a 50% cisplatin dose was given at the next cycle. If CrCl was >60 mL/min at end of cycle, full cisplatin dose was given at next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays

For diarrhea and stomatitis, see Table 1.

In the event of grade 2 or greater plantar-palmar toxicity, fluorouracil should be stopped until recovery. The fluorouracil dosage should be reduced by 20%.

For other greater than grade 3 toxicities, except alopecia and anemia, chemotherapy should be delayed (for a maximum of 2 weeks from the planned date of infusion) until resolution to grade ≤ 1 and then recommenced, if medically appropriate.

For other fluorouracil dosage adjustments, also refer to the manufacturers' prescribing information.

Combination Therapy with Strong CYP3A4 Inhibitors

Avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor [*see Drug Interactions (7), Clinical Pharmacology (12.3)*].

2.8 Administration Precautions

Docetaxel Injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel Injection solutions. The use of gloves is recommended. Please refer to [*see How Supplied/Storage and Handling (16.3)*].

If Docetaxel Injection or diluted solution for intravenous infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If Docetaxel Injection or diluted solution for intravenous infusion should come into contact with mucosa, immediately and thoroughly wash with water.

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

Docetaxel Injection requires dilution prior to administration.

Please follow the preparation instructions provided below.

2.9 Preparation and Administration

Docetaxel Injection (10 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Dilution for Infusion

1. Aseptically withdraw the required amount of Docetaxel Injection (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL.

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

2. Thoroughly mix the infusion by gentle manual rotation.
3. 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 or diluted solution is not clear or appears to have precipitation, it 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) 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 the 1 hour intravenous administration.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg/2 mL single use vial
- 80 mg/8 mL multi-use vial
- 160 mg/16 mL multi-use vial

4 CONTRAINDICATIONS

- Docetaxel Injection is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred [*see Warnings and Precautions (5.4)*].
- Docetaxel Injection should not be used in patients with neutrophil counts of <1500 cells/mm³.

5 WARNINGS AND PRECAUTIONS

5.1 Toxic Deaths

Breast Cancer

Docetaxel administered at 100 mg/m² 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/m², 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/m² 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/m² dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m² 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 combined abnormalities of transaminases and alkaline phosphatase should not be treated with Docetaxel Injection [*see Boxed Warning, Use in Specific Populations (8.6), Clinical Studies (14)*].

5.3 Hematologic Effects

Perform frequent peripheral blood cell counts on all patients receiving Docetaxel Injection. Patients should not be retreated with subsequent cycles of Docetaxel Injection until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level $>100,000$ cells/mm³.

A 25% reduction in the dose of Docetaxel Injection is recommended during subsequent cycles following severe neutropenia (<500 cells/mm³) 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/mm³) occurs in virtually all patients given 60 mg/m² to 100 mg/m² of docetaxel and grade 4 neutropenia (<500 cells/mm³) occurs in 85% of patients given 100 mg/m² and 75% of patients given 60 mg/m². 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/mm³.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m² but was very uncommon in patients given 60 mg/m².

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 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 Injection infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel Injection.

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)].

5.5 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/m². 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/m².

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).

5.6 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 [see *Clinical Studies (14.2)*]. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up.

5.7 Cutaneous Reaction

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.

5.8 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).

5.9 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.

5.10 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.

5.11 Use in Pregnancy

Docetaxel Injection 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 Injection. If Docetaxel Injection 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 Injection [see *Use in Specific Populations (8.1)*].

5.12 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/m² delivers 1.8 g/m² of ethanol. For a patient with a BSA of 2.0m², this would deliver 3.6 grams of ethanol [see *Description (11)*]. Other docetaxel products may have a different amount of alcohol.

6 ADVERSE REACTIONS

The most serious adverse reactions from docetaxel are:

- Toxic Deaths [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Hepatotoxicity [see *Boxed Warning, Warnings and Precautions (5.2)*]
- Neutropenia [see *Boxed Warning, Warnings and Precautions (5.3)*]
- Hypersensitivity [see *Boxed Warning, Warnings and Precautions (5.4)*]
- Fluid Retention [see *Boxed Warning, Warnings and Precautions (5.5)*]

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 Trial Experience

Breast Cancer

Monotherapy with docetaxel for locally advanced or metastatic breast cancer after failure of prior chemotherapy

Docetaxel 100 mg/m²: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administered at 100 mg/m² 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/m²

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	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
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	60
Severe	7	8	9
With 3-day Premedication	n=92	n=3	n=92
Any	64	67	64
Severe	7	33	7
Neurosensory			
Any	49	34	58
Severe	4	0	6
Cutaneous			
Any	48	54	47
Severe	5	10	5

Table 3 - Summary of Adverse Reactions in Patients Receiving Docetaxel at 100 mg/m²

Adverse Reaction	All Tumor Types Normal LFTs* n=2045 %	All Tumor Types Elevated LFTs** n=61 %	Breast Cancer Normal LFTs* n=965 %
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 $> 38^{\circ}\text{C}$ with intravenous antibiotics and/or hospitalization.

Hematologic Reactions

Reversible marrow suppression was the major dose-limiting toxicity of docetaxel [see *Warnings and Precautions* (5.3)]. The median time to nadir was 7 days, while the median duration of severe neutropenia (< 500 cells/mm³) 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/mm³ with fever $> 38^{\circ}\text{C}$ 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/mm³) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions

Severe hypersensitivity reactions have been reported [see *Boxed Warning, Warnings and Precautions* (5.4)]. 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 [*see Boxed Warning, Dosage and Administration (2.6), Warnings and Precautions (5.5)*].

Cutaneous Reactions

Severe skin toxicity is discussed elsewhere in the label [*see Warnings and Precautions (5.7)*]. 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.

Neurologic Reactions

Neurologic reactions are discussed elsewhere in the label [*see Warnings and Precautions (5.8)*].

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/m² in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by $\geq 10\%$ 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/m² 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

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/m² n=176 %	Best Supportive Care n=49 %	Vinorelbine/Ifosfamide n=119 %
Neuromotor			
Any	16	8	10
Grade 3/4	5	6	3
Skin			
Any	20	6	17
Grade 3/4	1	2	1
Gastrointestinal			
Nausea			
Any	34	31	31
Grade 3/4	5	4	8
Vomiting			
Any	22	27	22
Grade 3/4	3	2	6
Diarrhea			
Any	23	6	12
Grade 3/4	3	0	4
Alopecia	56	35	50
Asthenia			
Any	53	57	54
Severe***	18	39	23
Stomatitis			
Any	26	6	8
Grade 3/4	2	0	1
Pulmonary			
Any	41	49	45
Grade 3/4	21	29	19
Nail Disorder			
Any	11	0	2
Severe***	1	0	0
Myalgia			
Any	6	0	3
Severe***	0	0	0
Arthralgia			
Any	3	2	2
Severe***	0	0	1
Taste Perversion			
Any	6	0	0
Severe***	1	0	0

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

** Febrile Neutropenia: ANC grade 4 with fever $>38^{\circ}\text{C}$ 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 (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-Naïve Advanced Non-Small Cell Lung Cancer Patients Receiving Docetaxel in Combination with Cisplatin

Adverse Reaction	Docetaxel 75 mg/m² + Cisplatin 75 mg/m² n=406 %	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² 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

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

Adverse Reaction	Docetaxel 75 mg/m² + Cisplatin 75 mg/m² n=406 %	Vinorelbine 25 mg/m² + Cisplatin 100 mg/m² n=396 %
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia**		
Any	42	40
All severe or life-threatening events	5	5
Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia**		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder**		
Any	14	<1
All severe events	<1	0
Myalgia**		
Any	18	12
All severe events	<1	<1

* Replaces NCI Term "Allergy".

** COSTART term and grading system.

Deaths within 30 days of last study treatment occurred in 31 patients (7.6%) in the docetaxel+cisplatin arm and 37 patients (9.3%) in the vinorelbine+cisplatin arm. Deaths within 30 days of last study treatment attributed to study drug occurred in 9 patients (2.2%) in the docetaxel+cisplatin arm and 8 patients (2.0%) 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, [*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/m² 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)

Adverse Reaction	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 %	
	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/m² 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

Adverse Reaction	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	
	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 with Docetaxel Injection 75 mg/m² 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)

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

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)

Adverse Reaction (by Body System)	TAX323 (n=355)				TAX324 (n=494)			
	Docetaxel Injection arm (n=174)		Comparator arm (n=181)		Docetaxel Injection arm (n=251)		Comparator arm (n=243)	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %
Esophagitis/dysphagia/Odynophagia	13	1	18	3	25	13	26	10
Taste, sense of smell altered	10	0	5	0	20	0	17	1
Gastrointestinal pain/cramping	8	1	9	1	15	5	10	2
Heartburn	6	0	6	0	13	2	13	1
Gastrointestinal bleeding	4	2	0	0	5	1	2	1
Cardiac dysrhythmia	2	2	2	1	6	3	5	3
Venous***	3	2	6	2	4	2	5	4
Ischemia myocardial	2	2	1	0	2	1	1	1
Tearing	2	0	1	0	2	0	2	0
Conjunctivitis	1	0	1	0	1	0	0.4	0

Clinically important treatment emergent adverse reactions based upon frequency, severity, and clinical impact.

* Febrile neutropenia: grade ≥ 2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.

** Related to treatment.

*** Includes superficial and deep vein thrombosis and pulmonary embolism.

6.2 Post-Marketing Experiences

The following adverse reactions have been identified from clinical trials and/or post-marketing surveillance. Because they are reported from a population of unknown size, precise estimates of frequency cannot be made.

Body as a whole

Diffuse pain, chest pain, radiation recall phenomenon.

Cardiovascular

Atrial fibrillation, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism, syncope, tachycardia, myocardial infarction.

Cutaneous

Very rare cases of cutaneous lupus erythematosus and rare cases of bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and Scleroderma-like changes usually preceded by peripheral lymphedema. In some cases multiple factors may have contributed to the development of these effects. Severe hand and foot syndrome has been reported. Cases of permanent alopecia have 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 myelodysplastic 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.

7 DRUG INTERACTIONS

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

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection close monitoring for toxicity and a Docetaxel Injection dose reduction

could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

[*See Warnings and Precautions (5.11)*.]

Based on its mechanism of action and findings in animals, Docetaxel Injection can cause fetal harm when administered to a pregnant woman. If Docetaxel Injection 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 Injection.

Docetaxel Injection 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/m² 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.

8.3 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 Injection 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.

8.4 Pediatric Use

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

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

Docetaxel has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluorouracil (TCF).

Docetaxel Monotherapy

Docetaxel monotherapy was evaluated in a dose-finding phase 1 trial in 61 pediatric patients (median age 12.5 years, range 1-22 years) with a variety of refractory solid tumors. The recommended dose was 125 mg/m² 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/m² to 235 mg/m² 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/m².

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m² 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/m², 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 [*see Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

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

Non-Small Cell Lung Cancer

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

Breast Cancer

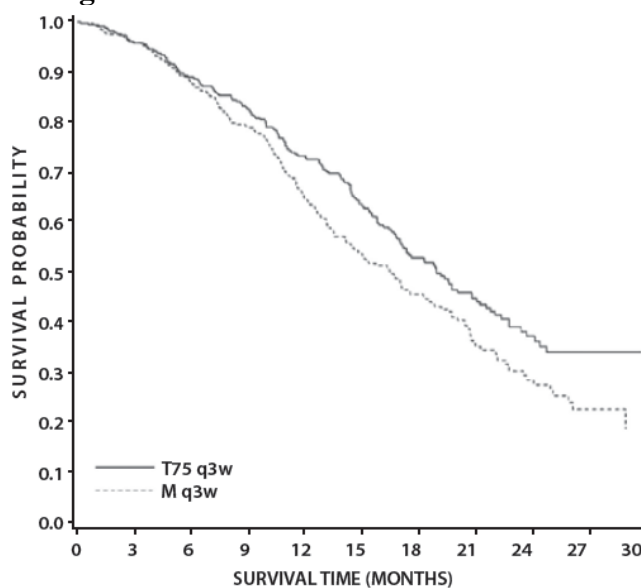
In the adjuvant breast cancer trial (TAX316), docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater.

Table 18 - Efficacy of Docetaxel in the Treatment of Patients with Androgen Independent (Hormone Refractory) Metastatic Prostate Cancer (Intent-to-Treat Analysis)

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

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

Figure 5 - TAX327 Survival K-M Curves



14.5 Gastric Adenocarcinoma

A multicenter, open-label, randomized trial was conducted to evaluate the safety and efficacy of Docetaxel Injection for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for advanced disease. A total of 445 patients with KPS >70 were treated with either Docetaxel Injection (T) (75 mg/m² on day 1) in combination with cisplatin (C) (75 mg/m² on day 1) and fluorouracil (F) (750 mg/m² per day for 5 days) or cisplatin (100 mg/m² on day 1) and fluorouracil (1000 mg/m² per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The demographic characteristics were balanced between the two treatment arms. The median age was 55 years, 71% were male, 71% were Caucasian, 24% were 65 years of age or older, 19% had a prior curative surgery and 12% had palliative surgery. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint and was defined as time from randomization to disease progression or death from any cause within 12 weeks of the last evaluable tumor assessment or within 12 weeks of the first infusion of study drugs for patients with no evaluable tumor assessment after randomization. The hazard ratio (HR) for TTP was 1.47 (CF/TCF, 95% CI: 1.19-1.83) with a significantly longer TTP (p=0.0004) in the TCF arm. Approximately 75% of patients had died at the time of this analysis. Overall survival was significantly longer (p=0.0201) in the TCF arm with a HR of 1.29 (95% CI: 1.04-1.61). Efficacy results are summarized in Table 19 and Figures 6 and 7.

Table 19 - Efficacy of Docetaxel Injection in the treatment of patients with gastric adenocarcinoma

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

* Unstratified log-rank test.

[†] For the hazard ratio (TCF/CF), values less than 1.00 favor the Docetaxel Injection arm. Subgroup analyses were consistent with the overall results across age, gender and race.

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

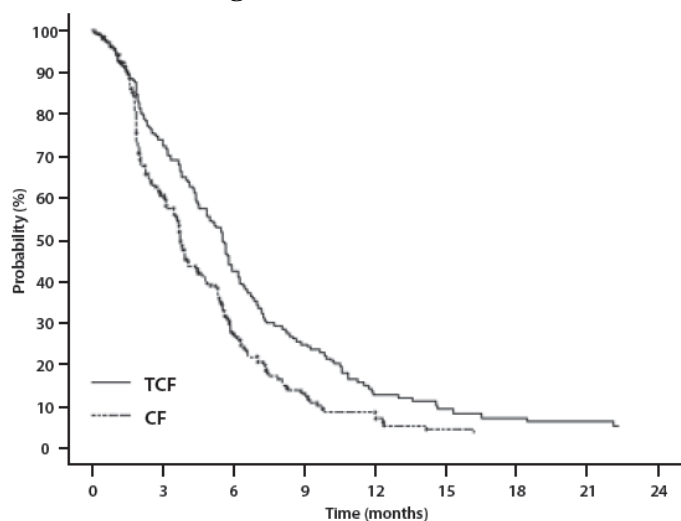
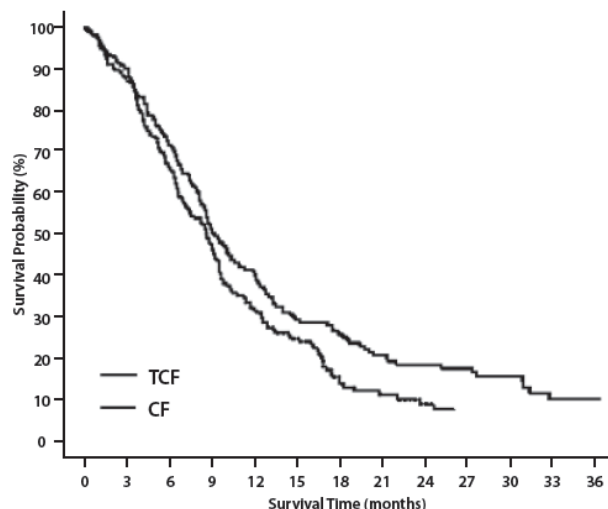


Figure 7 -Gastric Cancer Study (TAX325) Survival K-M Curve



14.6 Head and Neck Cancer

Induction Chemotherapy Followed by Radiotherapy (TAX323)

The safety and efficacy of Docetaxel Injection in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the Docetaxel Injection arm received Docetaxel Injection (T) 75 mg/m² followed by cisplatin (P) 75 mg/m² on Day 1, followed by fluorouracil (F) 750 mg/m² per day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m² on Day 1, followed by fluorouracil (F) 1000 mg/m²/day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with

a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines. Locoregional therapy with radiation was delivered either with a conventional fraction regimen (1.8 Gy-2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy) or with an accelerated/hyperfractionated regimen (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week, for a total dose of 70 to 74 Gy, respectively). Surgical resection was allowed following chemotherapy, before or after radiotherapy.

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

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

Endpoint	Docetaxel Injection+ Cisplatin+ Fluorouracil n=177	Cisplatin+ Fluorouracil n=181
Median progression free survival (months) (95% CI)	11.4 (10.1-14.0)	8.3 (7.4-9.1)
Adjusted Hazard ratio (95% CI)	0.71 (0.56-0.91)	
*p-value	0.0077	
Median survival (months) (95% CI)	18.6 (15.7-24.0)	14.2 (11.5-18.7)
Hazard ratio (95% CI)	0.71 (0.56-0.90)	
**p-value	0.0055	
Best overall response (CR + PR) to chemotherapy (%) (95% CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response (CR + PR) to study treatment [chemotherapy +/- radiotherapy] (%) (95% CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	

A Hazard ratio of less than 1 favors Docetaxel Injection+Cisplatin+Fluorouracil.

* Stratified log-rank test based on primary tumor site.

** Stratified log-rank test, not adjusted for multiple comparisons.

*** Chi square test, not adjusted for multiple comparisons.

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

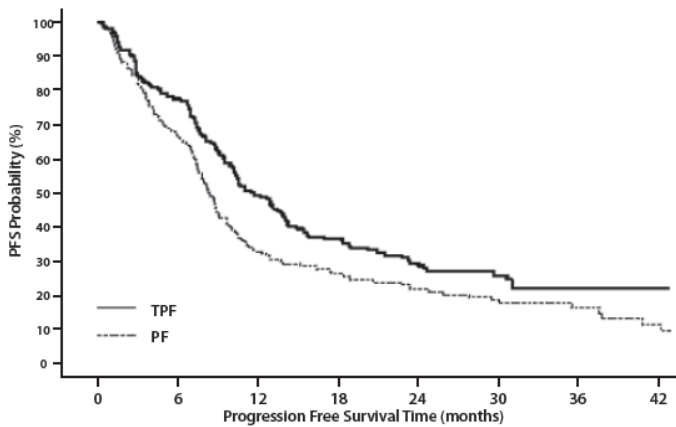
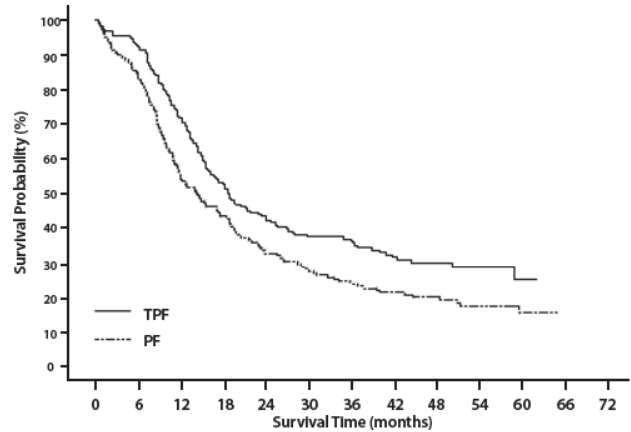


Figure 9 -TAX323 Overall Survival K-M Curve



Induction Chemotherapy Followed by Chemoradiotherapy (TAX324)

The safety and efficacy of Docetaxel Injection in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomized, multicenter open-label trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two treatment arms. Patients on the Docetaxel Injection arm received Docetaxel Injection (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles.

All patients in both treatment arms who did not have progressive disease were to receive 7 weeks of chemoradiotherapy (CRT) following induction chemotherapy 3 to 8 weeks after the start of the last cycle. During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT. The primary efficacy endpoint, overall survival (OS), was significantly longer (log-rank test, $p = 0.0058$) with the Docetaxel Injection-containing regimen compared to PF [median OS: 70.6 versus 30.1 months respectively, hazard ratio (HR) = 0.70, 95% confidence interval (CI) = 0.54 – 0.90]. Overall survival results are presented in Table 21 and Figure 10.

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

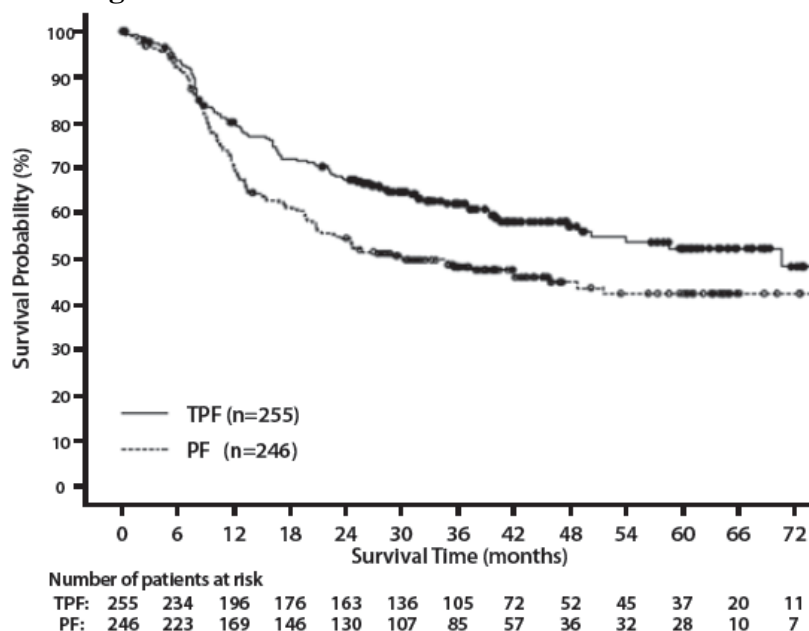
Endpoint	Docetaxel Injection+ Cisplatin+ Fluorouracil n=255	Cisplatin+ Fluorouracil n=246
Median overall survival (months) (95% CI)	70.6 (49.0-NE)	30.1 (20.9-51.5)
Hazard ratio: (95% CI)	0.70 (0.54-0.90)	
*p-value	0.0058	

A Hazard ratio of less than 1 favors Docetaxel Injection+cisplatin+fluorouracil.

* un-adjusted log-rank test.

NE - not estimable.

Figure 10 - TAX324 Overall Survival K-M Curve



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