SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Docetaxel Injection Concentrate (DAXOTEL**)**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Docetaxel anhydrous USP	20 mg
Polysorbate 80 (Purified)	520 mg
Ethanol Anhydrous USP	q.s
Citric Acid Anhydrous USP	q.s (to adjust pH)

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Breast Cancer
Docetaxel Injection Concentrate (DAXOTEL) is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.

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

Non-Small Cell Lung Cancer
DAXOTEL 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.

DAXOTEL in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer who have not previously received chemotherapy for this condition.

Prostate Cancer
DAXOTEL in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

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

Head and Neck Cancer

DAXOTEL 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).

4.2 Posology and Method of Administration

For all indications, toxicities may warrant dosage adjustments. Administer in a facility equipped to manage possible complications (e.g. anaphylaxis).

Breast Cancer

- For locally advanced or metastatic breast cancer after failure of prior chemotherapy, the recommended dose of docetaxel is 60 mg/m^2 to 100 mg/m^2 administered intravenously over 1 hour every 3 weeks.
- For the adjuvant treatment of operable node-positive breast cancer, the recommended docetaxel 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

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.

- For chemotherapy-naive patients, docetaxel was evaluated in combination with cisplatin. The recommended dose of docetaxel 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.

Prostate cancer

- For metastatic castration-resistant prostate cancer, the recommended dose of docetaxel is 75 mg/m^2 every 3 weeks as a 1 hour infusion. Prednisone 5 mg orally twice daily is administered continuously.

Gastric adenocarcinoma

- For gastric adenocarcinoma, the recommended dose of docetaxel 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.

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 containing arms of the studies received prophylactic antibiotics.

• *Induction chemotherapy followed by radiotherapy*
For the induction treatment of locally advanced inoperable SCCHN, the recommended dose of docetaxel 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.

• *Induction chemotherapy followed by chemoradiotherapy*
For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by 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

Premedication Regimen
All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

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 infusion.

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 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 therapy may tolerate higher doses. Patients who develop $\geq$ grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Combination Therapy with Docetaxel in the Adjuvant Treatment of Breast Cancer
Docetaxel in combination with doxorubicin and cyclophosphamide should be administered when the neutrophil count is $\geq$ 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 dose reduced to 60 mg/m^2. Patients who experience severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel therapy should have their dosage of docetaxel reduced from 75 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 *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 treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop $\geq$ grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Combination Therapy with Docetaxel for Chemotherapy-Naive NSCLC
For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, in patients who experience febrile neutropenia, and in patients with serious non-hematologic toxicities, the docetaxel dosage in subsequent cycles should be reduced to 65 mg/m^2. In patients who require a further dose reduction, a dose of 50 mg/m^2 is recommended.

Prostate Cancer

Combination Therapy with Docetaxel for metastatic castration-resistant prostate cancer
Docetaxel should be administered when the neutrophil count is $\geq$ 1,500 cells/mm^3. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or moderate neurosensory signs and/or symptoms during docetaxel therapy should have the dosage of docetaxel reduced from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Gastric or Head and Neck Cancer

Docetaxel in combination with cisplatin and fluorouracil in gastric cancer or head and neck cancer
Patients treated with docetaxel in combination with cispatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. In the study, 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 dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils

recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist.

Recommended dose modifications for gastrointestinal toxicities in patients treated with docetaxel in combination with cisplatin and fluorouracil are shown in Table No-1.

Table No-1 Recommended Dose Modifications for Gastrointestinal Toxicities in Patients Treated with Docetaxel in Combination with Cisplatin and Fluorouracil

Toxicity	**Dosage adjustment**
Diarrhea grade 3	First episode: reduce fluorouracil dose by 20 %. Second episode: then reduce docetaxel dose by 20 %.
Diarrhea grade 4	First episode: reduce docetaxel 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 dose by 20 %.
Stomatitis/mucositis grade 4	First episode: stop fluorouracil only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20 %.

Liver dysfunction:
In case of AST/ALT > 2.5 to $\leq$ 5 x UNL and AP $\leq$ 2.5 x UNL, or AST/ALT > 1.5 to $\leq$ 5 x UNL and AP > 2.5 to $\leq$ 5 x UNL, docetaxel should be reduced by 20 %.

In case of AST/ALT > 5 x UNL and/or AP > 5 x UNL docetaxel 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 $\geq$ 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 No-2):

Table No-2 Dose Reductions for Evaluation of Creatinine Clearance

Creatine 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 reinstituted 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 No-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 cisplatin and 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.

Administration Precautions
Docetaxel Injection concentrate is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel Injection concentrate solutions. The use of gloves is recommended.

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

Contact of the Docetaxel Injection concentrate 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 final Docetaxel Injection concentrate dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

One-vial Docetaxel Injection concentrate
Docetaxel Injection concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Please follow the preparation instructions provided below.

PREPARATION AND ADMINISTRATION

DO NOT use the two-vial formulation (Injection Concentrate and diluent) with the one-vial formulation.

One-vial Docetaxel Injection Concentrate

Docetaxel Injection concentrate (20 mg/ml) requires NO prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21 gauge needle to withdraw Docetaxel Injection concentrate from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.

1. Docetaxel Injection concentrate vials should be stored below 25°C. If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection concentrate vials to stand at room temperature for approximately 5 minutes before use.

2. Using only a 21gauge needle, aseptically withdraw the required amount of Docetaxel Injection concentrate (20 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 Injection concentrate is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

3. Thoroughly mix the infusion by gentle manual rotation.

4. As with all parenteral products, Docetaxel Injection concentrate should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel Injection concentrate dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded.

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

Stability:
Docetaxel Injection concentrate final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. Docetaxel Injection concentrate final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

4.3 Contraindications

Docetaxel is contraindicated in patients with:
- neutrophil counts of <1500 cells/mm^3
- a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80. Severe reactions, including anaphylaxis, have occurred

4.4 Special Warnings and Precautions for Use

Toxic Deaths

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

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

the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry.

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

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

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

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

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

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 co-administration 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.

Hypersensitivity Reactions
Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require

immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel. 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 infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of docetaxel.

Fluid Retention

Severe fluid retention has been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel administration to reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

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

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 and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies.

Cutaneous Reactions

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6 % (15/965) for metastatic breast cancer patients. Among 92

breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued docetaxel due to skin toxicity.

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

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

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.

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. 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. 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.

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.

Pediatric Use
The alcohol content of docetaxel Injection should be taken into account when given to pediatric patients. The efficacy of docetaxel in pediatric patients as monotherapy or in combination has not been established. The overall safety profile of docetaxel in pediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults. Docetaxel has been studied in a total of 289 pediatric patients: 239 in 2 trials with monotherapy and 50 in combination treatment with cisplatin and 5-fluoruracil (TCF).

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.

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

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Pregnancy Category D,
Based on its mechanism of action and findings in animals, docetaxel can cause fetal harm when administered to a pregnant woman. There are no adequate and well-control studies in pregnant women using docetaxel. If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during

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

Lactation
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 and for 1 week after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing
Verify pregnancy status in females of reproductive potential prior to initiating docetaxel.

Contraception

Females
Docetaxel can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of docetaxel.

Males
Based on genetic toxicity findings, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of docetaxel.

Infertility
Based on findings in animal studies, docetaxel may impair fertility in males of reproductive potential.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable Effects

The most serious adverse reactions from docetaxel are:

- Toxic Deaths
- Hepatic Impairment
- Hematologic Effects
- Enterocolitis and Neutropenic Colitis

- Hypersensitivity Reactions
- Fluid Retention
- Second Primary Malignancies
- Cutaneous Reactions
- Neurologic Reactions
- Eye Disorders
- Asthenia
- Alcohol Content

The most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Adverse reactions are described according to indication. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Clinical Trial Experience

Breast Cancer

Monotherapy with Docetaxel for Locally Advanced or Metastatic Breast Cancer after Failure of Prior Chemotherapy

Docetaxel 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks: 2045 patients with various tumor types and normal baseline liver function tests; the subset of 965 patients with locally advanced or metastatic breast cancer, both previously treated and untreated with chemotherapy, who had normal baseline liver function tests; and an additional 61 patients with various tumor types who had abnormal liver function tests at baseline.. 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 No-3).

Table No-3 Summary of Adverse Reactions in Patients Receiving Docetaxel at 100 mg/m^2

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

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

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

Hematologic Reactions

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

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

Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids. Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

Hypersensitivity Reactions
Severe hypersensitivity reactions are discussed in the boxed warning, precautions and warnings sections. 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 appropriate therapy.

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

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

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

Neurologic Reactions
Neurologic reactions are discussed elsewhere in the precautions and warnings section.

Gastrointestinal Reactions
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. 8.1 % (7/86) metastatic breast cancer patients receiving docetaxel 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by $\geq$ 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 is increased at higher doses and in patients with elevated baseline liver function tests

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

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

Combination Therapy with Docetaxel in the Adjuvant Treatment of Breast Cancer
The following treatment emergent adverse reactions observed in 744 patients, who were treated with docetaxel 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide.

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

Fever and Infection
Fever in the absence of infection was seen in 46.5% of TAC-treated patients and in 17.1% of FAC-treated patients. Grade 3/4 fever in the absence of infection was seen in 1.3% and 0% of

TAC- and FAC-treated patients respectively. Infection was seen in 39.4% of TAC-treated patients compared to 36.3% of FAC-treated patients. Grade 3/4 infection was seen in 3.9% and 2.2% of TAC-treated and FAC-treated patients respectively. There were no septic deaths in either treatment arm during the treatment period.

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

Cardiovascular Reactions
More cardiovascular reactions were reported in the TAC arm versus the FAC arm during the treatment period: arrhythmias, all grades (6.2% vs 4.9%), and hypotension, all grades (1.9% vs 0.8%). Twenty-six (26) patients (3.5%) in the TAC arm and 17 patients (2.3%) in the FAC arm developed CHF during the study period. All except one patient in each arm were diagnosed with CHF during the follow-up period. Two (2) patients in TAC arm and 4 patients in FAC arm died due to CHF. The risk of CHF was higher in the TAC arm in the first year, and then was similar in both treatment arms.

Adverse reactions during the follow-up period (median follow-up time of 8 years)
In study TAX316, the most common adverse reactions that started during the treatment period and persisted into the follow-up period in TAC and FAC patients are described below (median follow-up time of 8 years).

Nervous system disorders
In study TAX316, peripheral sensory neuropathy started during the treatment period and persisted into the follow-up period in 84 patients (11.3%) in TAC arm and 15 patients (2%) in FAC arm. At the end of the follow-up period (median follow-up time of 8 years), peripheral sensory neuropathy was observed to be ongoing in 10 patients (1.3%) in TAC arm, and in 2 patients (0.3%) in FAC arm.

Skin and subcutaneous tissue disorders
In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients (92.3%) and 645 of 736 FAC patients (87.6%). At the end of the follow-up period (actual median follow-up time of 8 years), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Reproductive system and breast disorders
In study TAX316, amenorrhea that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 202 of 744 TAC patients (27.2%) and 125 of 736 FAC patients (17.0%). Amenorrhea was observed to be ongoing at the end of the follow-up period (median follow-up time of 8 years) in 121 of 744 TAC patients (16.3%) and 86 FAC patients (11.7%).

General disorders and administration site conditions
In study TAX316, peripheral edema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was observed in 119 of 744 TAC patients (16.0%) and 23 of 736 FAC patients (3.1%). At the end of the follow-up period (actual median follow-up time of 8 years), peripheral edema was ongoing in 19 TAC patients (2.6%) and 4 FAC patients (0.5%).

In study TAX316, lymphedema that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 11 of 744 TAC patients (1.5%) and 1 of 736 FAC patients (0.1%). At the end of the follow-up period (actual median follow-up time of 8 years), lymphedema was observed to be ongoing in 6 TAC patients (0.8%) and 1 FAC patient (0.1%).

In study TAX316, asthenia that started during the treatment period and persisted into the follow-up period after the end of chemotherapy was reported in 236 of 744 TAC patients (31.7%) and 180 of 736 FAC patients (24.5%). At the end of the follow-up period (actual median follow-up time of 8 years), asthenia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).

Acute myeloid leukemia (AML)/Myelodysplastic syndrome (MDS)
AML occurred in the adjuvant breast cancer trial (TAX316). The cumulative risk of developing treatment-related AML at median follow-up time of 8 years in TAX316 was 0.4% for TAC-treated patients and 0.1% for FAC-treated patients. One TAC patient (0.1%) and 1 FAC patient (0.1%) died due to AML during the follow-up period (median follow-up time of 8 years). Myelodysplastic syndrome occurred in 2 of 744 (0.3%) patients who received TAC and in 1 of 736 (0.1%) patients who received FAC. AML occurs at a higher frequency when these agents are given in combination with radiation therapy.

Lung Cancer

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

Table No-4 Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving Docetaxel as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy*

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

***COSTART term and grading system

† Not Applicable; †† Not Done

Combination Therapy with Docetaxel in Chemotherapy-Naive Advanced Unresectable or Metastatic NSCLC

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

Weight gain Any All severe or life-threatening events	 15 <1	 9 <1
Neurosensory Any Grade 3/4	 47 4	 42 4
Neuromotor Any Grade 3/4	 19 3	 17 6
Skin Any Grade 3/4	 16 <1	 14 1
Nausea Any Grade 3/4	 72 10	 76 17
Vomiting Any Grade 3/4	 55 8	 61 16
Diarrhea Any Grade 3/4	 47 7	 25 3
Anorexia** Any All severe or life-threatening events	 42 5	 40 5
Stomatitis Any Grade 3/4	 24 2	 21 1
Alopecia Any Grade 3	 75 < 1	 42 0
Asthenia** Any All severe or life-threatening events	 74 12	 75 14
Nail Disorder** Any All severe events	 14 < 1	 <1 0
Myalgia** Any All severe events	 18 < 1	 12 < 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 section) 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 No-6).

Table No-6 Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with Prostate Cancer who Received Docetaxel in Combination with Prednisone

	Docetaxel 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %		**Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335 %**	
Adverse Reaction	**Any**	**G 3/4**	**Any**	**G 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* Weight Gain* Peripheral Edema*	24 8 18	1 0 0	5 3 2	0 0 0
Neuropathy Sensory	30	2	7	0
Neuropathy Motor	7	2	3	1
Rash/Desquamation	6	0	3	1
Alopecia	65	N/A	13	N/A

Nail Changes	30	0	8	0
Nausea	41	3	36	2
Diarrhea	32	2	10	1
Stomatitis/Pharyngitis	20	1	8	0
Taste Disturbance	18	0	7	0
Vomiting	17	2	14	2
Anorexia	17	1	14	0
Cough	12	0	8	0
Dyspnea	15	3	9	1
Cardiac left ventricular function	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

Gastric Cancer

Combination therapy with Docetaxel in gastric adenocarcinoma

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with docetaxel 75 mg/m^2 in combination with cisplatin and fluorouracil (see Table No-7).

Table No-7 Clinically Important Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in the Gastric Cancer Study

	Docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 n=221		**Cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 n=224**	
Adverse Reaction	**Any %**	**G3/4 %**	**Any %**	**G3/4 %**
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 event.
*Related to treatment

Head and Neck Cancer

Combination therapy with Docetaxel in head and neck cancer
Table No-8 summarizes the safety data obtained from patients that received induction chemotherapy with docetaxel 75 mg/m^2 in combination with cisplatin and fluorouracil followed by radiotherapy (Study A, 174 patients) or chemoradiotherapy (Study B, 251 patients).

Table No-8 Clinically Important Treatment Emergent Adverse Reactions (Regardless of Relationship) in Patients with SCCHN Receiving Induction Chemotherapy with Docetaxel in Combination with cisplatin and fluorouracil followed by radiotherapy or chemoradiotherapy

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

Others

The following adverse reactions have been identified from clinical trials. 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, 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. 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. Ventricular arrhythmia including ventricular tachycardia has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide, and may be associated with fatal outcome.

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: enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, has been reported with a potential fatal outcome. Abdominal pain, anorexia, constipation, duodenal ulcer, esophagitis, gastrointestinal hemorrhage, gastrointestinal perforation, intestinal obstruction, ileus, and dehydration as a consequence to gastrointestinal events have been reported.

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

Hematologic: bleeding episodes. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported.

Hepatic: rare cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Hypersensitivity: rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication. Hypersensitivity reactions with potential fatal outcome have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and nutrition disorders: electrolyte imbalance, including cases of hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia has 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. Cases of cystoid macular edema (CME) have been reported in patients treated with docetaxel.

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.

Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer, have been reported in patients treated with docetaxel-containing regimens.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

In mice, lethality was observed following single IV doses that were $\geq$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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

5.2 Pharmacokinetic Properties

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

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

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

Elimination: A study of ^{14}C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity,

respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Specific Populations

Effect of Age: A population pharmacokinetic analysis was carried out after docetaxel treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with docetaxel. Patients with severe hepatic impairment have not been studied.

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

Drug Interaction Studies

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m² intravenous) alone or docetaxel (10 mg/m² intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole.

Effect of Combination Therapies:
Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.

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

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

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

Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m²), doxorubicin (50 mg/m²), and cyclophosphamide (500 mg/m²) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis and Impairment of Fertility
Carcinogenicity studies with docetaxel have not been performed. Docetaxel was clastogenic in the *in vitro* chromosome aberration test in CHO-K1 cells and in the *in vivo* micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about $1/60^{th}$ to $1/15^{th}$ the recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polysorbate 80 (Purified)
Ethanol Anhydrous USP
Citric Acid Anhydrous USP

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C. Protect from light.

6.5 Nature and contents of container
DAXOTEL (Docetaxel Injection Concentrate), a single use, sterile, pyrogen-free, non-aqueous solution is supplied as 20 mg/1 ml in 6 ml glass vials, 80 mg/4 ml in 6 ml glass vials, 120 mg/6 ml in 6 ml glass vials, 160 mg/8 ml in 10 ml glass vials and 180 mg/9 ml in 10 ml glass vials.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anticancer drugs should be considered. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Docetaxel is a potential toxic compound and caution should be exercised while handling and preparing it.

- Use of protective gloves and clothing is recommended and only an expert should reconstitute the agent.
- In the event of the docetaxel concentrate, premix solution or infusion solution coming in direct contact with the skin, the skin should be washed immediately with soap and water. If they come into the direct contact with eye or sensitive mucous membranes they should be washed immediately and thoroughly with water.
- Adequate precautions and care should be taken while disposing off the items used to reconstitute the solution.

7. MARKETING AUTHORISATION HOLDER

Manufactured in India by:
Fresenius Kabi Oncology Ltd.
Village- Kishanpura,
P.O. Guru Majra,
Tehsil-Nalagarh,
Distt. Solan (H.P) -174101

8. MARKETING AUTHORISATION NUMBER (S)

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT: 04 SEP 2019

11. VERSION NUMBER: EXP/00/2019