SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TAXELDO 80 (Docetaxel Injection 80mg/4ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains Docetaxel (anhydrous)
20 mg for the full list of excipients, see
section 6.1

3. PHARMACEUTICAL FORM

Injection

Brownish yellow to pale yellow color solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

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

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

Docetaxel in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.
Gastric Adenocarcinoma

Docetaxel in combination with cisplatin and fluorouracil is indicated for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease.
Head and Neck Cancer
Docetaxel in combination with cisplatin and fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

4.2 Posology and method of Administration

Posology
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 intravenous 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 threeweeks. Patients must receive premedication with antiemetic and appropriate hydration for cisplatin administration.

Head and Neck Cancer

Patients must receive premedication with antiemetic, 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 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 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 Chemo radiotherapy (TAX324)

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 chemo radiotherapy.

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 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 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 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 grade 3 or 4 stomatitis should have their Docetaxel dose decreased 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 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, treatment should be discontinued.

Non-small Cell Lung Cancer

Monotherapy with Docetaxel 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^2 for more than one week, severe or cumulative cutaneous reactions, or other grade ¾ 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 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 counts 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. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Prostate Cancer

Combination therapy with Docetaxel for metastatic castration-resistant prostate cancer

Docetaxel should be administered when the neutrophil count is 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 mg/m^2 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 cisplatin and fluorouracil must receive antiemetic's 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 dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of Complicated neutropenia occur the Docetaxel dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia, the Docetaxel dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Do not retreat patients with subsequent cycles of Docetaxel until neutrophils recover to a level >1,500 cells/mm^3 [see Contraindications]. Avoid retreating patients until platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist. Recommended dose modifications for toxicities in patients treated with Docetaxel in combination with cisplatin and fluorouracil are shown in Table 1.

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

Toxicity	**Dosage adjustment**
Diarrhoea grade 3	First episode: reduce fluorouracil dose by 20%. Second episode: then reduce Docetaxel dose by 20%.
Diarrhoea 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 £5 × ULN and AP £2.5 × ULN, or AST/ALT >1.5 to £5 × ULN and AP >2.5 to £5 × ULN, Docetaxel should be reduced by 20%.
In case of AST/ALT >5 × ULN and/or AP >5 × ULN 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 NCI-CTCAE 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 × 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 ³60 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, fullcisplatin dose was given at next cycle.

CrCl = Creatinine clearance

Fluorouracil dose modifications and treatment delays For diarrhoea 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 anaemia, 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.
Administration Precautions

Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Docetaxel solutions. The use of gloves is recommended [see How Supplied/Storage and Handling].
If Docetaxel Injection 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 initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Contact of the Docetaxel 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 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)

Docetaxel Injection 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 and diluent) with the one-vial formulation. One-vial Docetaxel (Injection).
Docetaxel Injection (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 from the vial because larger bore needles (e.g., 18 and 19 gauge) may result in stopper coring and rubber particulates.
i)Docetaxel vials should be stored between 2°C and 25°C (36°F and 77°F). If the vials are stored under refrigeration, allow the appropriate number of vials of Docetaxel Injection vials to stand at room temperature for approximately 5 minutes before use.
ii) Using only a 21-gauge needle, aseptically withdraw the required amount of Docetaxel injection (20 mg docetaxel/mL) with a calibrated syringe and inject via a single injection (one shot) 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.
iii) Thoroughly mix the infusion by gentle manual rotation.

iv) As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the

v) v) Docetaxel dilution for intravenous infusion is not clear or appears to have precipitation, it should be discarded. Docetaxel infusion solution is supersaturated, therefore may crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.
Stability
Docetaxel final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 6 hours. Docetaxel final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 6 hours (including the 1-hour intravenous administration). In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36°F and 46°F).

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 Special warnings and precautions for use.

4.4 Special warnings and special 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/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/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 elevations of bilirubin or abnormalities of transaminase concurrent with alkaline

phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death.

Avoid Docetaxel in patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN.

For patients with isolated elevations of transaminase >1.5 × ULN, consider Docetaxel dose modifications.

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

Hematologic Effects

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

A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel cycle.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of Docetaxel and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^3. 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 coadministration of G-CSF.

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis and neutropenic enterocolitis may develop at any time, and could lead to death as early as the first day of symptom onset. Monitor patients closely from onset of any symptoms of gastrointestinal toxicity. Inform patients to contact their healthcare provider with new, or worsening symptoms of gastrointestinal toxicity.

Hypersensitivity Reactions

Monitor patients closely for hypersensitivity reactions, especially during the first and second infusions.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and aggressive therapy. Do not rechallenge patients with a history of severe hypersensitivity reactions 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 premeditated with oral corticosteroids prior to each Docetaxel administration to reduce the incidence and severity of fluid retention [see Dosage and Administration]. 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 (TAC) and in 1 of 736 patients who received fluorouracil, doxorubicin, and cyclophosphamide [see Clinical Studies]. In TAC-treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up. Monitor patients for second primary malignancies [see Adverse Reactions].

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]. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued Docetaxel due to skin toxicity.

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

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]. 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 [see Clinical Pharmacology]. 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. Each administration of Docetaxel Injection at 100 mg/m^2 delivers 2.0 g/m^2 of ethanol. For a patient with a BSA of 2.0 m^2, this would deliver 4.0 grams of ethanol. Other docetaxel products may have a different amount of alcohol.

Tumor Lysis Syndrome

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

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 co-administered 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

Risk Summary

Based on findings in 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. Docetaxel contains alcohol, which can interfere with neurobehavioral development. In animal reproductive studies, administration of docetaxel to pregnant rats and rabbits during the period of organogenesis caused an increased incidence of embryo-fetal toxicities, including intrauterine mortality, at doses as low as 0.02 and 0.003 times the recommended human dose based on body surface area, respectively [see Data]. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, miscarriage, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Clinical Considerations

Docetaxel contains alcohol Published studies have demonstrated that alcohol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development.

Data Animal data

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

Lactation

Risk Summary

There is no information regarding the presence of docetaxel in human milk, or on its effects on milk Production or the breastfed child. No lactation studies in animals have been conducted. Because of the potential for serious adverse

reactions in a breastfed child, advise women not to breastfeed during treatment with Docetaxel 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 Docetaxe

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

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 paediatric patients receiving monotherapy or TCF was consistent with the known safety profile in adults.

Docetaxel has been studied in a total of 289 paediatric 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/m^2 as a 1-hour intravenous infusion every 21 days. The primary dose limiting toxicity was neutropenia.

The recommended dose for Docetaxel monotherapy was evaluated in a phase 2 single-arm trial in 178 pediatric patients (median age 12 years, range 1–26 years) with a variety of recurrent/refractory solid tumors. Efficacy was not established with tumor response rates ranging from one complete response (CR) (0.6%) in a patient with undifferentiated sarcoma to four partial responses (2.2%) seen in one patient each with Ewing Sarcoma, neuroblastoma, osteosarcoma, and squamous cell carcinoma.

Docetaxel in Combination

Docetaxel was studied in combination with cisplatin and 5-fluorouracil (TCF) versus cisplatin and 5-fluorouracil (CF) for the induction treatment of nasopharyngeal carcinoma (NPC) in pediatric patients prior to chemo radiation consolidation. Seventy-five patients (median age 16 years, range 9 to 21 years) were randomized (2:1) to Docetaxel (75 mg/m^2) in combination with cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2) (TCF) or to cisplatin (80 mg/m^2) and 5-fluorouracil (1000 mg/m^2/day) (CF).

The primary endpoint was the CR rate following induction treatment of NPC. One patient out of 50 in the TCF group (2%) had a complete response while none of the 25 patients in the CF group had a complete response.

Pharmacokinetics

Pharmacokinetic parameters for docetaxel were determined in 2 pediatric solid tumor trials. Following docetaxel administration at 55 mg/m^2 to 235 mg/m^2 in a 1-hour intravenous infusion every 3 weeks in 25 patients aged 1 to 20 years (median 11 years), docetaxel clearance was 17.3±10.9 L/h/m^2.

Docetaxel was administered in combination with cisplatin and 5-fluorouracil (TCF), at dose levels of 75 mg/m^2 in a 1-hour intravenous infusion day 1 in 28 patients aged 10 to 21 years (median 16 years, 17 patients were older than 16). Docetaxel clearance was 17.9±8.75 L/h/m^2, corresponding to an AUC of 4.20±2.57 µg·h/mL.

In summary, the body surface area adjusted clearance of docetaxel monotherapy and TCF combination in children were comparable to those in adults.

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-naive 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-naive, 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 ³10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs 59%), infection (37% vs 24%), nail changes (34% vs 23%), anorexia (21%
vs 10%), weight loss (15% vs 5%), respectively.

Breast Cancer

In the adjuvant breast cancer trial (TAX316), Docetaxel in combination with doxorubicin and Cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater.
The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.
Gastric Cancer

Among the 221 patients treated with Docetaxel in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse reactions was higher in the elderly patients compared to younger patients. The incidence of the following adverse reactions (all grades, regardless of relationship): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates ³10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.
Head and Neck Cancer

Among the 174 and 251 patients who received the induction treatment with Docetaxel in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, 18 (10%) and 32 (13%) of the patients were 65 years of age or older, respectively.
These clinical studies of Docetaxel in combination with cisplatin and fluorouracil in patients with SCCHN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has not identified differences in responses between elderly and younger patients.

Hepatic Impairment

Avoid Docetaxel in patients with bilirubin >ULN and patients with AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN.
The alcohol content of Docetaxel Injection should be taken into account when given to patients with hepatic impairment.

4.7 Effects on ability to drive and use machines

Docetaxel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most serious undesirable effects 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 Studies 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 tumour 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 tumour types who had abnormal liver function tests at baseline. These reactions were described using COSTART terms and were considered possibly or probably related to Docetaxel . At least 95% of these patients did not receive hematopoietic support. The safety profile is generally similar in patients receiving Docetaxel for the treatment of breast cancer and in patients with other tumor types. (See Table 3.)

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

Adverse Reaction	All Tumor Types Normal LFTs* 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	31	41	35
Any			
Severe	2	8	2
Hypersensitivity Reactions Regardless of Premedication	21	20	18
Any			
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 £1.5 times ULN or alkaline phosphatase £2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

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

>2.5 times ULN

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

Hematologic reactions

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

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

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

Hypersensitivity reactions

Severe hypersensitivity reactions have been reported [see Boxed Warning,

Warnings and Precautions]. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and instituting appropriate therapy.

Fluid retention

Fluid retention can occur with the use of Docetaxel .

Cutaneous reactions

Severe skin toxicity is discussed elsewhere in the label.

Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after Docetaxel infusion, recovered before the next infusion, and were not disabling.

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

Neurologic reactions

Neurologic reactions are discussed elsewhere in the label.

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 have occurred. Seven of 86 (8.1%) of metastatic breast cancer patients receiving Docetaxel 100 mg/m^2 in a randomized trial and who had serial leftventricular ejection fractions assessed developed deterioration of LVEF by 10% associated with a drop below the institutional lower limit of normal.

Infusion site reactions

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

Hepatic reactions

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

Hematologic and other toxicity: Relation to dose and baseline liver chemistry

abnormalities Hematologic and other toxicity is increased at higher doses and in patients with elevated baseline liver function tests (LFTs). In the following tables, adverse drug reactions are compared for three populations: 730 patients with normal LFTs given Docetaxel at 100 mg/m^2 in the randomized and single arm studies of metastatic breast cancer after failure of previous chemotherapy; 18 patients in these studies who had abnormal baseline LFTs (defined as AST and/or ALT >1.5 times ULN concurrent with alkaline phosphatase >2.5 times ULN); and 174 patients in Japanese studies given Docetaxel at 60 mg/m^2 who had normal LFTs (see Tables 4 and 5).

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

	Docetaxel 100 mg/m^2		**Docetaxel 60 mg/m^2**
	Normal LFTs* n=730 %	**Elevated LFTs† n=18 %**	**Normal LFTs* n=174 %**
Neutropenia			
Any <2000 cells/mm^3	98	100	95
Grade4 <500 cells/mm^3	84	94	75
Thrombocytopenia			
Any <100,000 cells/mm^3	11	44	14
Grade 4 <20,000 cells/mm^3	1	17	1
Anemia <11 g/dL	95	94	65
Infection‡			
Any	23	39	1
Grade 3 and 4	7	33	0
Febrile Neutropenia§			
By Patient	12	33	0
By Course	2	9	0
Septic Death	2	6	1
Non-Septic Death	1	11	0

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

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

>2.5 times ULN

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

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

Table 5: Non-hematologic Adverse Reactions in Breast Cancer Patients

Previously Treated with Chemotherapy Treated at Docetaxel 100 mg/m² with Normal or Elevated Liver Function Tests or 60 mg/m² with Normal Liver Function Tests.

Adverse Reaction	Docetaxel 100 mg/m²		Docetaxe l 60 mg/m²
	Normal LFTs* n=730 %	Elevated LFTs† n=18 %	Normal LFTs* n=174 %
Acute Hypersensitivity Reaction Regardless of Premedication			
Any	13	6	1
Severe	1	0	0
Fluid Retention‡ Regardless of Premedication			
Any	56	61	13
Severe	8	17	0
Neurosensory			
Any	57	50	20
Severe	6	0	0
Myalgia	23	33	3
Cutaneous			
Any	45	61	31
Severe	5	17	0
Asthenia			
Any	65	44	66
Severe	17	22	0
Diarrhea			
Any	42	28	NA
Severe	6	11	
Stomatitis			
Any	53	67	19
Severe	8	39	1

NA = not available

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

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

‡Fluid Retention includes (by COSTART): edema (peripheral, localized, generalized, lymphedema, Pulmonary edema, and edema otherwise not specified) and effusion (pleural, pericardial, and ascites);no premedication given with the 60 mg/m² dose.

In the three-arm monotherapy trial, TAX313, which compared Docetaxel 60 mg/m², 75 mg/m² and 100 mg/m² in advanced breast cancer, grade 3/4 or severe adverse reactions occurred in 49.0% of patients treated with Docetaxel 60 mg/m² compared to 55.3% and 65.9% treated with 75 mg/m² and 100 mg/m², respectively. Discontinuation due to adverse reactions was reported in 5.3% of patients treated with 60 mg/m² versus 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 mg/m^2, 75 mg/m^2, 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 table presents treatment-emergent adverse reactions observed in 744 patients, who were treated with Docetaxel 75 mg/m^2 every 3 weeks in combination with doxorubicin and cyclophosphamide (see Table 6).

Table 6: Clinically Important Treatment-Emergent Adverse Reactions Regardless of Causal Relationship in Patients Receiving Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAX316).

	Docetaxel 75 mg/m^2 +Doxorubicin 50 mg/m^2 +		**Fluorouracil 500 mg/m^2 + Doxorubicin 50 mg/m^2 +**	
Adverse Reaction	Any	Grade 3/4	Any	Grade 3/4
Anemia	92	4	72	2
Neutropenia	71	66	82	49
Fever in absence	47	1	17	0
Infection	39	4	36	2
Thrombocytopen	39	2	28	1
Febrile	25	N/A	3	N/A
Neutropenic	12	N/A	6	N/A
Hypersensitivity	13	1	4	0
Lymphedema	4	0	1	0
Fluid Retention*	35	1	15	0
Peripheral edema	27	0	7	0
Weight gain	13	0	9	0
Neuropathy	26	0	10	0
Neuro-cortical	5	1	6	1
Neuropathy	4	0	2	0
Neuro-cerebellar	2	0	2	0
Syncope	2	1	1	0
Alopecia	98	N/A	97	N/A

Skin toxicity	27	1	18	0
Nail disorders	19	0	14	0
Nausea	81	5	88	10
Stomatitis	69	7	53	2
Vomiting	45	4	59	7
Diarrhea	35	4	28	2
Constipation	34	1	32	1
Taste perversion	28	1	15	0
Anorexia	22	2	18	1
Abdominal Pain	11	1	5	0
Amenorrhea	62	N/A	52	N/A
Cough	14	0	10	0
Cardiac	8	0	6	0
Vasodilatation	27	1	21	1
Hypotension	2	0	1	0
Phlebitis	1	0	1	0
Asthenia	81	11	71	6
Myalgia	27	1	10	0
Arthralgia	19	1	9	0
Lacrimation	11	0	7	0
Conjunctivitis	5	0	7	0

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

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

Fever and infection

During the treatment period, 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 reactions reflected in the table above, 7 patients in the TAC arm were reported to have colitis/enteritis/large intestine perforation versus 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 8years) 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-upperiod 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-treate 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 for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy Docetaxel 75 mg/m^2: Treatment-emergent adverse drug reactions are shown in Table 7. Included in this table are safety data for a total of 176 patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who were treated in two randomized, controlled trials. These reactions were described using NCI Common Toxicity Criteria regardless of relationship to study treatment, except for the hematologic toxicities or where otherwise noted.

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

	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 Grade 3/4	91 9	55 12	91 14
Febrile Neutropenia†	6	NA‡	1
Infection Any Grade 3/4	34 10	29 6	30 9
Treatment Related Mortality	3	NA‡	3
Hypersensitivity Reactions Any Grade 3/4	6 3	0 0	1 0
Fluid Retention Any Severe	34 3	ND§	23 3
Neurosensory Any Grade 3/4	23 2	14 6	29 5
Neuromotor Any Grade 3/4	16 5	8 6	10 3
Skin Any Grade 3/4	20 1	6 2	17 1
Gastrointestinal **Nausea** Any	34	31	31
Grade 3/4	5	4	8
Vomiting Any Grade 3/4	22 3	27 2	22 6
Diarrhea Any Grade 3/4	23 3	6 0	12 4
Alopecia	56	35	50
Asthenia Any Severe¶	53 18	57 39	54 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	1	0	0
Any			
severe			
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 £1.5 times ULN or alkaline phosphatase £2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

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

‡Not Applicable

§Not Done

¶COSTART term and grading system

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

Table 8 presents safety data from two arms of an open label, randomized controlled trial (TAX326) that enrolled patients with unresectable stage IIIB or IV non-small cell lung cancer and no history of prior chemotherapy. Adverse reactions were described using the NCI Common Toxicity Criteria except where otherwise noted.

	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
Events		2
Peripheral edema		
Any	34	18
All severe or life-threatening events	<1	<1
Weight gain		
Any	15	9
All severe or life-threatening events	<1	<1
Neurosensory		
Any	47	42
Grade 3/4	4	4
Neuromotor		
Any	19	17
Grade 3/4	3	6
Skin		
Any	16	14
Grade 3/4	<1	1
Nausea		
Any	72	76
Grade 3/4	10	17
Vomiting		
Any	55	61
Grade 3/4	8	16
Diarrhea		
Any	47	25
Grade 3/4	7	3
Anorexia†		
Any	42	40
All severe or life-threatening events	5	5

Stomatitis		
Any	24	21
Grade 3/4	2	1
Alopecia		
Any	75	42
Grade 3	<1	0
Asthenia†		
Any	74	75
All severe or life-threatening events	12	14
Nail Disorder†		
Any	14	<1
All severe events	<1	0
Myalgia†		
Any	18	12
All severe events	<1	<1

*Replaces NCI term "Allergy"

†COSTART term and grading system

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

The second comparison in the study, vinorelbine+cisplatin versus Docetaxel +carboplatin (which did not demonstrate a superior survival associated with Docetaxel demonstrated a higher incidence of thrombocytopenia, diarrhea, fluid retention, hypersensitivity reactions, skin toxicity, alopecia and nail changes on the Docetaxel +carboplatin arm, while a higher

incidence of anemia, neurosensory toxicity, nausea, vomiting, anorexia and asthenia was observed on the vinorelbine+cisplatin arm.

Prostate Cancer

Combination therapy with Docetaxel in patients with prostate cancer

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

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

	Docetaxel 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=332 %	**Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n=335**

Adverse Reaction	Any	Grade 3/4	Any	Grade
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	10	0	22	1
Fatigue	53	5	35	5
Myalgia	15	0	13	1
Tearing	10	1	2	0
Arthralgia	8	1	5	1

*Related to treatment

Gastric Cancer

Combination therapy with Docetaxel in gastric adenocarcinoma

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

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

	Docetaxel 75 mg/m² + cisplatin 75 mg/m² + fluorouracil 750 mg/m² n=221		**Cisplatin 100 mg/m² + fluorouracil 1000 mg/m² n=224**	
Adverse Reaction	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Anemia	97	18	93	26
Neutropenia	96	82	83	57
Fever in the absence of infection	36	2	23	1
Thrombocytopenia	26	8	39	14
Infection	29	16	23	10
Febrile neutropenia	16	N/A	5	N/A
Neutropenic infection	16	N/A	10	N/A
Allergic reactions	10	2	6	0
Fluid retention*	15	0	4	0
Edema*	13	0	3	0
Lethargy	63	21	58	18
Neurosensory	38	8	25	3
Neuromotor	9	3	8	3
Dizziness	16	5	8	2
Alopecia	67	5	41	1
Rash/itch	12	1	9	0
Nail changes	8	0	0	0
Skin desquamation	2	0	0	0

Nausea	73	16	76	19
Vomiting	67	15	73	19
Anorexia	51	13	54	12
Stomatitis	59	21	61	27
Diarrhea	78	20	50	8
Constipation	25	2	34	3
Esophagitis/ dysphagia/ odynophagia	16	2	14	5
Gastrointestinal pain/ cramping	11	2	7	3
Cardiac dysrhythmias	5	2	2	1
Myocardial ischemia	1	0	3	2
Tearing	8	0	2	0
Altered hearing	6	0	13	2

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

Head and Neck Cancer

Combination therapy with Docetaxel in head and neck cancer

Table 11 summarizes the safety data obtained from patients that received induction chemotherapy with Docetaxel 75 mg/m² in combination with cisplatin and fluorouracil followed by radiotherapy (TAX323; 174 patients) or chemo radiotherapy (TAX324; 251 patients). The treatment regimens are described in Section 14.6.

	TAX323 (n=355)				**TAX324 (n=494)**			
	Docetaxel arm (n=174)		**Comparator arm (n=181)**		**Docetaxel arm (n=251)**		**Comparator arm (n=243)**	
Adverse Reaction (by Body System)	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %	Any %	Grade 3/4 %
Neutropenia	93	76	87	53	95	84	84	56
Anemia	89	9	88	14	90	12	86	10
Thrombocytopenia	24	5	47	18	28	4	31	11
Infection	27	9	26	8	23	6	28	5

Febrile neutropenia*	5	N/A	2	N/A	12	N/A	7	N/A
Neutropenic infection	14	N/A	8	N/A	12	N/A	8	N/A
Cancer pain	21	5	16	3	17	9	20	11
Lethargy	41	3	38	3	61	5	56	10
Fever in the absence of infection	32	1	37	0	30	4	28	3
Myalgia	10	1	7	0	7	0	7	2
Weight loss	21	1	27	1	14	2	14	2
Allergy	6	0	3	0	2	0	0	0
Fluid retention†	20	0	14	1	13	1	7	2
Edema only	13	0	7	0	12	1	6	1
Weight gain only	6	0	6	0	0	0	1	0
Dizziness	2	0	5	1	16	4	15	2
Neurosensory	18	1	11	1	14	1	14	0
Altered hearing	6	0	10	3	13	1	19	3
Neuromotor	2	1	4	1	9	0	10	2
Alopecia	81	11	43	0	68	4	44	1
Rash/itch	12	0	6	0	20	0	16	1
Dry skin	6	0	2	0	5	0	3	0
Desquamation	4	1	6	0	2	0	5	0
Nausea	47	1	51	7	77	14	80	14
Stomatitis	43	4	47	11	66	21	68	27
Vomiting	26	1	39	5	56	8	63	10
Diarrhea	33	3	24	4	48	7	40	3
Constipation	17	1	16	1	27	1	38	1
Anorexia	16	1	25	3	40	12	34	12
Esophagitis/ dysphagia/ Odynophagia	13	1	18	3	25	13	26	10
Taste, sense of smell altered	10	0	5	0	20	0	17	1
Gastrointestinal pain/cramping	8	1	9	1	15	5	10	2
Heartburn	6	0	6	0	13	2	13	1
Gastrointestinal bleeding	4	2	0	0	5	1	2	1

Cardiac dysrhythmia	2	2	2	1	6	3	5	3

Venous‡	3	2	6	2	4	2	5	4
Ischemia myocardial	2	2	1	0	2	1	1	1
Tearing	2	0	1	0	2	0	2	0
Conjunctivitis	1	0	1	0	1	0	0.4	0

Clinically important treatment-emergent adverse reactions based upon frequency, severity, and clinical impact.
*Febrile neutropenia: grade 2 fever concomitant with grade 4 neutropenia requiring intravenous antibiotics and/or hospitalization.
†Related to treatment.

‡Includes superficial and deep vein thrombosis and pulmonary embolism

Post marketing Experience

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

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

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

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

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

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

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

Hepatic: hepatitis, sometimes fatal, primarily in patients with pre-existing liver disorders. **Hypersensitivity:** anaphylactic shock with fatal outcome in patients who received premedication. Severe hypersensitivity reactions with fatal outcome with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and nutrition disorders: electrolyte imbalance, including hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia. Tumor lysis syndrome, sometimes fatal.
Neurologic: confusion, seizures or transient loss of consciousness, sometimes appearing during the infusion of the drug.
Ophthalmologic: conjunctivitis, lacrimation or lacrimation with or without conjunctivitis, cystoid macular edema (CME). Excessive tearing which may be attributable to lacrimal duct obstruction. Transient visual disturbances (flashes, flashing lights, scotomata), typically occurring during drug infusion and reversible upon discontinuation of the infusion, in association with hypersensitivity reactions.
Respiratory: dyspnea, acute pulmonary edema, acute respiratory distress syndrome/pneumonitis, Interstitial lung disease, interstitial pneumonia, respiratory failure, and pulmonary fibrosis, which may be fatal. Radiation pneumonitis in patients receiving concomitant radiotherapy.
Renal: renal insufficiency and renal failure, the majority of cases were associated with concomitant Nephrotoxic drugs.
Second primary malignancies: second primary malignancies, including AML, MDS, NHL, and renal cancer.
Musculoskeletal disorder: myositis.

Reporting of suspected adverse reactions:

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)https://pv.pharmacyboardkenya.org

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 over dosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.
In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.
In mice, lethality was observed following single intravenous doses that were □154 mg/kg (about 4.5

times the human dose of 100 mg/m^2 on a mg/m^2 basis); neurotoxicity associated with paralysis, non-extension of hind limbs, and myelin degeneration was observed in mice at 48 mg/kg (about 1.5
times the human dose of 100 mg/m^2 basis). In male and female rats, lethality was observed at a dose of 20 mg/kg (comparable to the human dose of 100 mg/m^2 on a mg/m^2 basis) and was associated with abnormal mitosis and necrosis of multiple organs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

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

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of docetaxel has been evaluated in cancer patients after administration of 20mg/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 a, b, and g 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 a1-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 14C-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 was 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 Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.
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/m^2 intravenous) alone or docetaxel (10 mg/m^2 intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administered 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/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination.

The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

Docetaxel has been shown to be genotoxic by an aneugenic mechanism in the *in vitro* micronucleus and chromosome aberration test in CHO K1 cells and in the *in*

vivo micronucleus test in the mouse. However, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. These results are consistent with the pharmacological activity of docetaxel.

Undesirable effects on the testis observed in rodent toxicity studies suggest that docetaxel may impair male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients:

Polysorbate 80 (Montanox 80 LPI), Dehydrated alcohol (Ethanol).

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store between 2°C- 8°C. Protect from light.

6.5 Nature and contents of pack's

1x1 vial pack

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORIZATION HOLDER

Hetero Labs Limited
7-2-A2, Hetero Corporate, Industrial Estates
Sanath Nagar, Hyderabad, Zip-500 018,
Telangana

8. MARKETING AUTHORIZATION NUMBER

H2025/CTD11607/24979

9. DATE OF FIRST REGISTRATION / RENEWAL OF THE REGISTRATION

2025 May 01

10. DATE OF REVISION OF THE TEXT

2025 May 01