

## DOCETAXEL



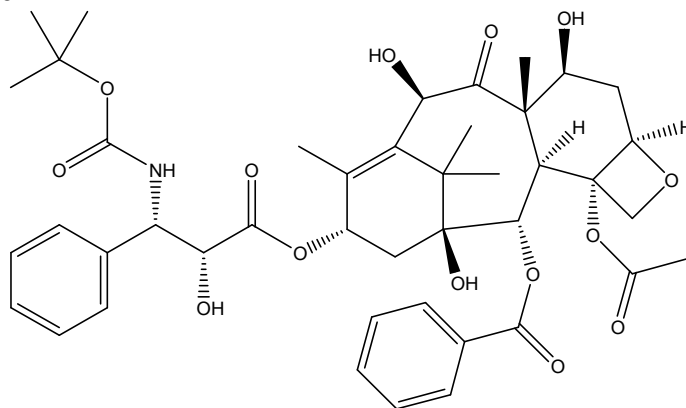
10 mg/mL Solution for Infusion (IV)

### 1.0 PHARMACOLOGIC CATEGORY

Antineoplastic Agent (Taxane)

### 2.0 DESCRIPTION

#### Chemical structure



Chemical name: (2*R*,3*S*)-*N*-carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β, 20-epoxy-1,2α,4,7β,10β,13α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate.

Molecular formula: C<sub>43</sub>H<sub>53</sub>NO<sub>14</sub>

Molecular weight: 807.88

Docetaxel is a white to off-white powder. It is highly lipophilic and practically insoluble in water.

#### CAS number

114977-28-5

Each 1 mL Docetaxel 10 mg/mL Solution for Infusion (IV) contains 10 mg docetaxel and it is supplied as a 20 mg/2 mL and 80 mg/8 mL concentrated injection vial.

Excipients with known effect:

- Ethanol (see **Section 4.4 Special warnings and precautions for use, Alcohol content**).

For the full list of excipients, see **Section 6.1 List of excipients**.

### 3.0 FORMULATION/COMPOSITION

Solution for Infusion.

Docetaxel 10 mg/mL Solution for Infusion (IV) is a sterile clear, colorless to pale yellow solution free from visible particulates. It must be diluted prior to intravenous administration.

## **4.0 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Docetaxel 10 mg/mL Solution for Infusion (IV) is indicated for:

#### **Breast Cancer**

##### ***Metastatic Breast Cancer***

Treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed.

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

##### ***Adjuvant Treatment of Breast Cancer***

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with node positive breast cancer.

Doxorubicin and cyclophosphamide followed by Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2.

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with carboplatin and trastuzumab (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2.

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with cyclophosphamide is indicated for the adjuvant treatment of operable breast cancer with a primary tumor of  $\geq 1$  cm and  $< 7$  cm.

#### **Non-Small Cell Lung Cancer**

Treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum-based chemotherapy.

#### **Ovarian Cancer**

Treatment of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.

## Prostate Cancer

Treatment of patients with androgen independent (hormone refractory) prostate cancer.

## Head and Neck Cancer

Docetaxel 10 mg/mL Solution for Infusion (IV) in combination with cisplatin and fluorouracil (TPF), is indicated as induction treatment prior to chemoradiotherapy, for the treatment of patients with locally advanced, squamous cell carcinoma of the head and neck, who have low probability of surgical cure, require organ preservation or where the tumor is technically unresectable.

## 4.2 Dosage and method of administration

### Dosage

#### *Breast cancer*

##### Metastatic breast cancer

##### *Monotherapy*

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 to 100 mg/m<sup>2</sup> administered as a one-hour infusion every three weeks (see **Preparation for the intravenous administration**). A dose of 100 mg/m<sup>2</sup> of docetaxel has been shown to result in a moderate increase in response rates compared with 75 mg/m<sup>2</sup> but is associated with greater toxicity.

##### *Combination with Capecitabine*

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 mg/m<sup>2</sup> administered as a one-hour infusion every three weeks when combined with capecitabine administered orally at 1,250 mg/m<sup>2</sup> twice daily (within 30 minutes after the end of a meal) for two weeks followed by a 1-week rest period, given as 3-week cycles. Refer to capecitabine Product Information for capecitabine dose calculation according to body surface area.

##### *Combination with trastuzumab (HER2+)*

For the docetaxel plus trastuzumab combination, the recommended Docetaxel 10 mg/mL Solution for Infusion (IV) dose is 100 mg/m<sup>2</sup> every three weeks, with trastuzumab administered weekly. For trastuzumab dosage and administration, see the trastuzumab Product Information leaflet.

##### Adjuvant treatment of breast cancer

##### *Combination with doxorubicin and cyclophosphamide*

The recommended dose of Docetaxel 10 mg/mL Solution for Infusion (IV) in the adjuvant treatment of breast cancer is 75 mg/m<sup>2</sup> administered 1 hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for a total of six cycles (TAC regimen) (see also **Dosage adjustments during treatment** and **Section 4.4 Special warnings and precautions for use**).

##### *Combination with trastuzumab following doxorubicin and cyclophosphamide (HER2+)*

AC-TH. AC (cycles 1-4): doxorubicin (A) 60 mg/m<sup>2</sup> followed by cyclophosphamide (C) 600 mg/m<sup>2</sup> administered every three weeks for 4 cycles.

TH (cycles 5-8): docetaxel (T) 100 mg/m<sup>2</sup> administered every three weeks for 4 cycles, and trastuzumab (H) administered weekly according to the following schedule:

Cycle 5 (starting three weeks after the last cycle of AC). Day 1: trastuzumab 4 mg/kg (loading dose); day 2: docetaxel 100 mg/m<sup>2</sup>; days 8 and 15: trastuzumab 2 mg/kg.

Cycles 6-8. Day 1: docetaxel 100 mg/m<sup>2</sup> and trastuzumab 2 mg/kg; days 8 and 15: trastuzumab 2 mg/kg.

Three weeks after day 1 of cycle 8: trastuzumab 6 mg/kg is given every three weeks.

Trastuzumab is administered for a total duration of 1 year.

*Combination with carboplatin and trastuzumab (HER2+)*

TCH. TCH (cycles 1-6): docetaxel (T) 75 mg/m<sup>2</sup> and carboplatin (C) at AUC of 6 mg/mL/min administered every three weeks and trastuzumab (H) administered weekly according to the following schedule:

Cycle 1. Day 1: trastuzumab 4 mg/kg (loading dose); day 2: docetaxel 75 mg/m<sup>2</sup> and carboplatin at AUC of 6 mg/mL/min; days 8 and 15: trastuzumab 2 mg/kg.

Cycles 2-6. Day 1: docetaxel 75 mg/m<sup>2</sup> followed by carboplatin at AUC of 6 mg/mL/min and trastuzumab 2 mg/kg; days 8 and 15: trastuzumab 2 mg/kg.

Three weeks after day 1 of cycle 6: trastuzumab 6 mg/kg is given every three weeks.

Trastuzumab is administered for a total duration of 1 year.

*Combination with Cyclophosphamide*

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 mg/m<sup>2</sup> over 1 hour and cyclophosphamide 600 mg/m<sup>2</sup> as an intravenous administration over 30 to 60 minutes on day 1 of a 21-day cycle for a total of four cycles. Premedication with oral dexamethasone 8 mg twice daily is administered commencing 1 day before administering Docetaxel 10 mg/mL Solution for Infusion (IV), and continuing for a total of five doses.

***Non-small cell lung cancer***

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 to 100 mg/m<sup>2</sup> administered as a one-hour infusion every three weeks (see **Preparation for the intravenous administration**). A dose of 100 mg/m<sup>2</sup> of docetaxel has been shown to result in a moderate increase in response rates compared with 75 mg/m<sup>2</sup> but is associated with greater toxicity.

***Ovarian cancer***

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 to 100 mg/m<sup>2</sup> administered as a one-hour infusion every three weeks (see **Preparation for the intravenous administration**). A dose of 100 mg/m<sup>2</sup> of docetaxel has been shown to result in a moderate increase in response rates compared with 75 mg/m<sup>2</sup> but is associated with greater toxicity.

## ***Prostate cancer***

### ***Metastatic castration-resistant prostate cancer***

The recommended dosage of Docetaxel 10 mg/mL Solution for Infusion (IV) for prostate cancer is 75 mg/m<sup>2</sup> administered as a one-hour infusion every three weeks. Prednisone or prednisolone 5 mg orally twice daily is administered continuously, commencing day 1 and continuing through each cycle.

## ***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. For cisplatin and fluorouracil dose modifications, see manufacturers' Product Information.

### **Induction chemotherapy followed by radiotherapy (TAX 323)**

For the induction treatment of locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 mg/m<sup>2</sup> as a one-hour infusion followed by cisplatin 75 mg/m<sup>2</sup> over one hour on day 1, followed by fluorouracil as a continuous infusion at 750 mg/m<sup>2</sup>/day for five days. This regimen is administered every three weeks for four cycles. Following chemotherapy, patients should receive radiotherapy.

### **Induction chemotherapy followed by chemoradiotherapy (TAX 324)**

For the induction treatment of patients with locally advanced (unresectable, low surgical cure or organ preservation) SCCHN, the recommended dose of Docetaxel 10 mg/mL Solution for Infusion (IV) is 75 mg/m<sup>2</sup> as a one-hour IV infusion on day 1, followed by cisplatin 100 mg/m<sup>2</sup> administered as a 30-minute to three-hour infusion, followed by fluorouracil 1,000 mg/m<sup>2</sup> as a continuous infusion from day 1 to day 4. This regimen is administered every three weeks for three cycles. Following chemotherapy, patients should receive chemoradiotherapy.

## ***Premedication in breast, non-small cell lung, ovarian and head and neck cancers***

A premedication consisting of an oral corticosteroid, e.g. dexamethasone 16 mg/day (e.g. 8 mg twice daily) for three days starting one day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

## ***Premedication in prostate cancer***

For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg 12 hours, three hours and one hour before the docetaxel infusion.

## ***Dosage adjustments during treatment***

Docetaxel 10 mg/mL Solution for Infusion (IV) should be administered when the neutrophil count is greater than or equal to  $1.5 \times 10^9$  cells/L.

### ***In patients treated at 75 mg/m<sup>2</sup>***

Patients who experienced either febrile neutropenia, neutrophils  $< 0.5 \times 10^9$  cells/L for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during docetaxel therapy should have the dosage of docetaxel reduced from 75 mg/m<sup>2</sup> to 55 mg/m<sup>2</sup> (or to 60 mg/m<sup>2</sup> for adjuvant therapy for breast cancer). If the patient continues to experience these reactions at 55 mg/m<sup>2</sup> (or at 60 mg/m<sup>2</sup>), the treatment should be discontinued.

***In patients treated at 100 mg/m<sup>2</sup>***

Patients who experienced either febrile neutropenia, neutrophils  $< 0.5 \times 10^9$  cells/L for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during docetaxel therapy should have the dosage of docetaxel reduced from 100 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup>. If the patient continues to experience these reactions at 75 mg/m<sup>2</sup>, either the dosage should be decreased from 75 mg/m<sup>2</sup> to 55 mg/m<sup>2</sup> or the treatment should be discontinued.

***Patients treated with docetaxel in combination with Capecitabine***

For capecitabine dose modifications when combined with docetaxel, see capecitabine Product Information.

For patients developing the first appearance of a grade 2 toxicity which persists at the time of the next docetaxel/capecitabine treatment, delay treatment until resolved to grade 0 to 1, and resume at 100% of the original dose.

For patients developing the second appearance of a grade 2 toxicity, or the first appearance of a grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to grade 0 to 1, then resume treatment with docetaxel 55 mg/m<sup>2</sup>.

For any subsequent appearances of toxicities, or any grade 4 toxicities, discontinue the docetaxel dose.

***Patients treated with docetaxel in combination with trastuzumab***

For the docetaxel plus trastuzumab combination, the recommended Docetaxel 10 mg/mL Solution for Infusion (IV) dose is 100 mg/m<sup>2</sup> every three weeks, with trastuzumab administered weekly. For trastuzumab dosage and administration, see trastuzumab Product Information.

***Patients treated with docetaxel in combination with doxorubicin and cyclophosphamide***

In the docetaxel, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up (see **Section 4.8 Undesirable effects**).

Primary G-CSF prophylaxis should be considered in patients who receive TAC adjuvant therapy for breast cancer. Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience febrile neutropenia and/or neutropenic infection should remain on G-CSF and have their docetaxel dose reduced to 60 mg/m<sup>2</sup>. If G-CSF is not used, the docetaxel dose should be reduced from 75 to 60 mg/m<sup>2</sup>. Patients who experience grade 3 or 4 stomatitis should have their dose decreased to 60 mg/m<sup>2</sup>.

***Patients treated with docetaxel in AC-TH or TCH***

Patients who received AC-TH or TCH adjuvant therapy for operable breast cancer whose tumors overexpress HER2 and who experience an episode of febrile neutropenia or infection should receive prophylactic G-CSF in all subsequent cycles. For a second episode of febrile neutropenia or infection, patients should continue prophylactic G-CSF, and docetaxel will be reduced from 100 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup> (in the AC-TH regimen); docetaxel will be reduced from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> (in the TCH regimen).

However, in clinical practice neutropenia could occur in cycle 1. Thus, G-CSF should be used in consideration of the neutropenic risk of the patient and current recommendations. Depending on the treatment regimen, patients who experience grade 3 or 4 stomatitis should have their dose decreased from 100 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup> (in the AC-TH regimen) or from 75 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> (in the TCH regimen).

***Patients treated with docetaxel in combination with cisplatin and fluorouracil in head and neck cancer***

Patients treated with docetaxel in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. G-CSF should be administered to mitigate the risk of complicated neutropenia.

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<sup>2</sup>. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m<sup>2</sup>.

In case of grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m<sup>2</sup>. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm<sup>3</sup> and platelets recover to a level > 100,000 cells/m<sup>3</sup>. Discontinue treatment if these toxicities persist.

For cisplatin and fluorouracil dosage and administration, see the relevant Product Information.

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**

<b>Toxicity</b>	<b>Dosage adjustment</b>
Diarrhea grade 3	1 <sup>st</sup> episode: reduce fluorouracil (FU) dose by 20% 2 <sup>nd</sup> episode: then reduce docetaxel dose by 20%
Diarrhea grade 4	1 <sup>st</sup> episode: reduce docetaxel and fluorouracil (FU) doses by 20% 2 <sup>nd</sup> episode: discontinue treatment
Stomatitis/mucositis grade 3	1 <sup>st</sup> episode: reduce fluorouracil (FU) dose by 20% 2 <sup>nd</sup> episode: stop fluorouracil (FU) only, at all subsequent cycles 3 <sup>rd</sup> episode: reduce docetaxel dose by 20%
Stomatitis/mucositis grade 4	1 <sup>st</sup> episode: stop fluorouracil (FU) only, at all subsequent cycles 2 <sup>nd</sup> episode: reduce docetaxel dose by 20%

***Use in renal impairment***

No information available.

***Use in hepatic impairment***

**Patients with hepatic impairment in patients treated at 75 mg/m<sup>2</sup>**

For those patients with increased serum bilirubin and/or values > 3.5 times the upper limit of

normal (ULN) for ALT and AST and > six times the ULN for alkaline phosphatase, no dose reduction can be recommended and docetaxel should not be used unless strictly indicated.

In patients treated at 100 mg/m<sup>2</sup>

Based on the pharmacokinetic data, in patients who have both elevations of transaminase values (ALT and/or AST greater than 1.5 times the ULN and increases in alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m<sup>2</sup> (see **Section 5.2 Pharmacokinetic properties**). For those patients with increased serum bilirubin and/or values > 3.5 times the ULN for ALT and AST and > six times the ULN for alkaline phosphatase, no dose reduction can be recommended and docetaxel should not be used unless strictly indicated.

For capecitabine dosage reduction when combined with docetaxel, see capecitabine Product Information.

***Dialysis***

No information available.

***Concomitant disease***

No information available.

***Maximum tolerated daily dose and the maximum dose for an entire course of therapy***

The maximum daily dose is 100mg/m<sup>2</sup>. The maximum dose per course is not specified.

***Monitoring advice***

Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel.

***Use in children***

The safety and effectiveness of docetaxel in children have not been established.

***Use in the elderly***

Based on the population pharmacokinetics, there are no special instructions for use in the elderly.

For capecitabine dosage reduction when combined with docetaxel see capecitabine Product Information.

**Instruction For Use/Handling**

As with all parenteral products, Docetaxel 10 mg/mL Solution for Infusion (IV) should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

Contact of Docetaxel 10 mg/mL Solution for Infusion (IV) 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 10 mg/mL Solution for Infusion (IV) dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

### ***Preparation and storage of the infusion solution***

Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding volume from the appropriate number of vials using a graduated syringe fitted with a needle. For example, a dose of docetaxel 140 mg would require 14 mL Docetaxel 10 mg/mL Solution for Infusion (IV) .

Inject the required volume into a 250 mL infusion bag or bottle containing either sodium chloride 0.9% solution or glucose 5% solution. If a dose greater than docetaxel 200 mg is required, use a larger volume of the infusion vehicle so that a concentration of docetaxel 0.74 mg/mL is not exceeded. Mix the infusion bag or glass bottle manually using a rocking motion.

Docetaxel 10 mg/mL Solution for Infusion (IV) should be aseptically administered intravenously as a one-hour infusion under room temperature and normal lighting conditions. The solution for infusion is stable at room temperature (25°C) for up to four hours. However, to reduce microbiological hazards and the risk of crystallization of docetaxel from diluted solutions, it is recommended that dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the solution for infusion. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Any residue after infusion should be discarded. Any solutions which are discolored, hazy or contain visible particulate matter should not be used.

*Disposal.* All materials that have been utilized for dilution and administration should be disposed of according to standard procedures.

### ***Recommendations for Safe Handling***

Docetaxel 10 mg/mL Solution for Infusion (IV) is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing docetaxel solutions. The use of gloves is recommended.

If Docetaxel 10 mg/mL Solution for Infusion (IV) or docetaxel infusion solution comes into contact with the skin, wash immediately and thoroughly with soap and water. If Docetaxel 10 mg/mL Solution for Infusion (IV) or docetaxel infusion solution comes into contact with mucous membranes, wash immediately and thoroughly with water.

Each presentation must be diluted prior to intravenous administration. Use in one patient on one occasion only.

## **4.3 Contraindications**

History of severe hypersensitivity reactions to docetaxel or any of the excipients.

Baseline neutrophil count of  $< 1.5 \times 10^9$  cells/L.

Severe liver impairment.

Pregnant or breastfeeding women.

Contraindications that apply for other drugs also apply when these drugs are combined with Docetaxel 10 mg/mL Solution for Infusion (IV).

## 4.4 Special warnings and precautions for use

The use of Docetaxel 10 mg/mL Solution for Infusion (IV) should be confined to units specialized in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist.

### Premedication

Patients should be pre-treated prior to each Docetaxel 10 mg/mL Solution for Infusion (IV) administration. A premedication consisting of an oral corticosteroid, e.g. dexamethasone 16 mg/day (e.g. 8 mg twice daily) for three days starting one day prior to Docetaxel 10 mg/mL Solution for Infusion (IV) administration, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **Fluid Retention and Hypersensitivity Reactions**, below; also see **Section 4.2 Dosage and method of administration**).

For prostate cancer, the premedication is oral dexamethasone 8 mg, 12 hours, three hours and one hour before the docetaxel infusion.

### Hematology

Bone marrow suppression and other hematological effects of docetaxel include neutropenia, the most frequent adverse effect of docetaxel (see **Section 4.8 Undesirable effects - Clinical Studies**). Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted in all patients receiving docetaxel. Patients should be retreated with docetaxel only when neutrophils recover to a level greater than or equal to  $1.5 \times 10^9/\text{L}$ .

Docetaxel 10 mg/mL Solution for Infusion (IV) should not be administered to patients with baseline neutrophil counts of  $<1.5 \times 10^9$  cells/L. Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel. Patients should not be retreated with Docetaxel 10 mg/mL Solution for Infusion (IV) until neutrophils recover to a level greater than or equal to  $1.5 \times 10^9$  cells/L (see **Section 4.2 Dosage and method of administration**).

In the case of severe neutropenia ( $<0.5 \times 10^9$  cells/L for seven days or more) during a course of Docetaxel 10 mg/mL Solution for Infusion (IV) therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures is recommended. Prophylactic G-CSF may be used to mitigate the risk of hematological toxicities.

Patients treated with TPF and TAC should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel 10 mg/mL Solution for Infusion (IV) dose reduced (see **Section 4.2 Dosage and method of administration - Dosage adjustments during treatment**). Patients receiving TPF and TAC should be closely monitored (see **Section 4.2 Dosage and method of administration** and **Section 4.8 Undesirable effects**).

In the treatment of adjuvant breast cancer, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow-up (see **Section 4.8 Undesirable effects**).

### Gastrointestinal Reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications (see **Section 4.2 Dosage and method of administration**, **Section 4.4 Special warnings and precautions for use - Hematology** and **Section 4.8 Undesirable effects**). Although majority of cases occurred during the first or second cycle of docetaxel containing regimen, enterocolitis could develop at any time, and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity.

### **Hypersensitivity Reactions**

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes of, during or immediately following the cessation of the infusion of Docetaxel 10 mg/mL Solution for Infusion (IV), thus facilities for the treatment of hypotension and bronchospasm should be available. Frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnea and drug fever or chills. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalized rash/erythema, require immediate discontinuation of Docetaxel 10 mg/mL Solution for Infusion (IV) and aggressive therapy. Severe symptoms are usually resolved after discontinuing the infusion and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with Docetaxel 10 mg/mL Solution for Infusion (IV). Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of docetaxel therapy.

### **Cutaneous Reactions**

Reversible cutaneous reactions were generally mild to moderate. Reactions were characterized by a rash including localized eruptions mainly on feet, hands (including severe hand and foot syndrome), but also arms, face or thorax, and frequently associated with pruritus. Eruptions generally occurred within one week after the docetaxel infusion. Less frequently, severe symptoms, e.g. eruptions followed by desquamation which rarely led to interruption or discontinuation of docetaxel treatment were reported. Nail disorders were characterized by hypopigmentation or hyperpigmentation, pain and onycholysis.

Very rare cases of cutaneous lupus erythematosus and bullous eruptions, e.g. erythema multiforme, scleroderma-like changes and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear, discontinuation of docetaxel should be considered. In some cases, multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects.

### **Ear and Labyrinth Disorders**

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

### **Eye Disorders**

Cystoid macular edema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case cystoid macular edema is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated.

### **Fluid Retention**

A premedication consisting of an oral corticosteroid, e.g. dexamethasone 16 mg/day (e.g. 8 mg twice daily) for three days starting one day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **Section 4.2 Dosage and method of administration**).

The peripheral edema usually starts at the lower extremities and may become generalized with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity; however, it has been reported in some patients during early courses of therapy. The median cumulative dose to onset for treatment with 75 mg/m<sup>2</sup> is 524 mg/m<sup>2</sup> and treatment at 100 mg/m<sup>2</sup> is 509 mg/m<sup>2</sup> (without premedication) and 797 mg/m<sup>2</sup> (with premedication). Fluid retention is slowly reversible after docetaxel treatment is stopped. In patients treated by docetaxel as single agent at 100 mg/m<sup>2</sup>, the median cumulative dose to treatment discontinuation was more than 1,000 mg/m<sup>2</sup> and the median time to fluid retention reversibility was 16.4 weeks (range 0 to 42 weeks).

Fluid retention has not been accompanied by acute episodes of oliguria or hypotension. Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored more closely.

Patients developing peripheral edema may be treated with standard measures.

### **Respiratory Disorders**

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of docetaxel therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated.

### **Nervous System**

The development of severe neurosensory signs and/or symptoms have been observed in patients and require a reduction of dose (see **Section 4.2 Dosage and method of administration**).

### **Cardiac Toxicity**

Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin and epirubicin) containing chemotherapy. This may be moderate to severe and has been associated with death.

When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment. Cardiac function should be further monitored

during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction.

### **Tumor lysis syndrome**

Tumor lysis syndrome has been reported with docetaxel after the first or the second cycle (see **Section 4.8 Undesirable effects**). Patients at risk of tumor lysis syndrome (e.g. with renal impairment, hyperuricemia, bulky tumor, rapid progression) should be closely monitored. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

### **CYP3A4 Inhibitors**

The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see **Section 4.5 Interactions with other medicinal products and other forms of interaction**).

### **Additional cautions for use in adjuvant treatment of breast cancer**

#### *Complicated neutropenia*

For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G-CSF and dose reduction should be considered (see **Section 4.2 Dosage and method of administration**).

#### *Gastrointestinal reactions*

Early abdominal pain and tenderness, fever, diarrhea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.

#### *Congestive heart failure (CHF)*

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period.

In patients treated with the TAC regimen for node positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see **Section 4.8 Undesirable effects**).

#### *Leukemia*

In the adjuvant treatment of breast cancer, the risk of delayed myelodysplasia or myeloid leukemia requires hematological follow up.

### **Alcohol Content**

Docetaxel 10 mg/mL Solution for Infusion (IV) contains ethanol.

The alcohol content is harmful for those suffering from alcoholism.

The alcohol content is to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Consideration should be given to possible effects on the central nervous system.

Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to

accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity.

### **Use in Hepatic Impairment**

Liver function tests (LFTs) should be measured at baseline and before each cycle. In patients treated with docetaxel at 100 mg/m<sup>2</sup> who have both elevations of serum transaminase values (ALT and/or AST) > 1.5 times the upper limit of normal and increases in alkaline phosphatase > 2.5 times the upper limit of normal, there is a greater risk of developing severe adverse effects such as toxic deaths including sepsis, gastrointestinal hemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. The recommended dose of docetaxel in patients with elevated LFTs is 75 mg/m<sup>2</sup> (see **Section 4.2 Dosage and method of administration**).

For patients with increased serum bilirubin and/or values > 3.5 times the upper limit of normal for ALT and AST, and > 6 times the upper limit of normal for alkaline phosphatase, no dose reduction can be recommended and docetaxel should not be used unless strictly indicated.

No data are available in patients with hepatic impairment treated by docetaxel in combination therapy.

### **Use in Renal Impairment**

There are no data available in patients with severely impaired renal function treated with docetaxel.

### **Use in the Elderly**

An analysis of safety data in patients equal to or greater than 60 years of age treated with docetaxel in combination with capecitabine showed an increase in the incidence of treatment-related grade 3 or 4 adverse effects, treatment related serious adverse effects and early withdrawals from treatment due to adverse effects compared to patients less than 60 years of age.

### ***Use in castration-resistant prostate cancer***

Of the 333 patients treated with docetaxel every three weeks for metastatic castration-resistant prostate cancer in the prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. Differences in efficacy were not identified between elderly patients and younger patients. In patients treated with docetaxel every three weeks, the incidence of anemia, infection, nail changes, anorexia, weight loss occurred at rates ≥10% higher in patients who were 65 years of age or greater compared to younger patients.

### ***Use in adjuvant treatment of breast cancer***

There are no data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide.

The proportion of elderly patients was 5.5% and 6.6% in the AC-TH and TCH regimens, respectively, and is too limited to allow for conclusions regarding the adverse events occurring by age (< 65 years vs. greater than or equal to 65 years).

Of the 174 and 251 patients who received the induction treatment with docetaxel in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX 323 and TAX 324 studies, only 18 (10%) and 32 (13%), respectively, of the patients were 65 years of age or older.

The number of elderly patients who received this regimen was not sufficient to determine whether geriatric patients responded differently from younger patients. Elderly patients treated with TPF should be closely monitored.

### **Pediatric Use**

The safety and effectiveness of docetaxel in children have not been established.

### **Effects on Laboratory Tests**

No data available.

## **4.5 Interactions with other medicinal products and other forms of interaction**

There have been no formal clinical studies to evaluate the drug interactions of docetaxel.

*In vitro* studies suggest that isoenzymes of the cytochrome P450-3A subfamily appear to be involved in the hepatic metabolism of docetaxel in humans. *In vitro*, the biotransformation of docetaxel was inhibited by ciclosporin, terfenadine, ketoconazole, erythromycin and troleandomycin and to a lesser extent by doxorubicin, vinorelbine, vinblastine and nifedipine, increased by dexamethasone, phenobarbitone and clofibrate and unaffected by cimetidine, ranitidine, omeprazole, diazepam, imipramine, paracetamol, caffeine, tolbutamide and quinidine. Strong P450-3A inhibitors may affect docetaxel metabolism *in vivo*, necessitating caution in co-administration regimens.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration.

In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49%. In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided. If the concomitant use of a strong CYP3A4 inhibitor cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during concomitant treatment with the strong CYP3A4 inhibitor.

*In vitro*, plasma protein binding was more than 95%, with the important proteins being albumin, alpha1-acid glycoprotein and lipoproteins. The *in vitro* plasma protein binding of docetaxel was not affected by dexamethasone, erythromycin, salicylate, sulfamethoxazole, diphenhydramine, propranolol, propafenone, phenytoin and sodium valproate. The binding of digitoxin was not affected by docetaxel.

*In vivo* investigations show that caution should be exercised when administering ketoconazole to patients as concomitant therapy since there is a potential for a significant interaction.

Docetaxel should be administered with caution in patients concomitantly receiving protease inhibitors (e.g. ritonavir) which are inhibitors and substrates of cytochrome P450-3A.

The amount of alcohol in this medicinal product may alter the effects of other medicinal

products.

## **4.6 Fertility, pregnancy and lactation**

### **Effects on fertility**

Studies in mice have shown that intravenous doses of 144 mg/m<sup>2</sup> or 30 mg/m<sup>2</sup>/day for five days are associated with testicular atrophy, mineralization and degeneration of tubular germinal epithelium, Leydig cell hyperplasia and epididymal hypospermia and follicular atresia in the ovaries. Studies in rats have shown that intravenous doses of 120 mg/m<sup>2</sup> are associated with testicular atrophy, germ cell atrophy, Leydig cell hyperplasia and mineralization. The rodent studies suggest that docetaxel may impair fertility. Studies in rats have also shown that intravenous doses of 0.9 mg/m<sup>2</sup>/day to both sexes are associated with reduced litter averages for corpora lutea, implantations and live fetuses, and increased litter averages for early and total resorptions. Larger doses to both sexes (males 1.8 mg/m<sup>2</sup>/day, females 1.35 mg/m<sup>2</sup>/day) are additionally associated with increased time to mating, increased number of dams with total resorption, and reduced male fetal bodyweight.

An adverse effect on male or female fertility cannot be excluded. Therefore, men being treated with docetaxel are advised to seek advice on conservation of sperm prior to treatment, and all patients intending to have a child after treatment are advised to consider individual genetic counselling.

### **Use in pregnancy – Category D**

Docetaxel may cause fetal harm when administered to a pregnant woman. Therefore, docetaxel must not be used during pregnancy.

Fetal radioactivity has been detected following intravenous administration of radiolabelled docetaxel to pregnant rats. Docetaxel has been shown to be embryotoxic and fetotoxic in rats and rabbits. At intravenous doses of 0.9 mg/m<sup>2</sup>, docetaxel caused fewer corpora lutea, fewer implantations, increased resorptions and embryofetal deaths in rats. No evidence of teratogenic effects was found when docetaxel was administered intravenously at doses up to 1.8 mg/m<sup>2</sup> or 1.2 mg/m<sup>2</sup> in rats or rabbits, respectively, but reduced fetal weight and delayed ossification were observed.

Offspring from rats receiving docetaxel 1.5 mg/m<sup>2</sup>/day intravenously from late gestation until weaning showed signs of delayed development. No studies have been performed in pregnant women.

If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with this drug and to inform the treating physician immediately should this occur.

### **Contraception in males and females**

Based on reproductive toxicity and genetic toxicity findings, women of childbearing potential should be advised to use effective contraception during treatment with docetaxel and for at least 6 months after the last dose.

Based on genetic toxicity findings, male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with docetaxel and for at

least 3 months after the last dose.

### Use in lactation

Radioactivity has been detected in milk following intravenous administration of radiolabelled docetaxel to lactating rats. Offspring from rats receiving docetaxel 1.5 mg/m<sup>2</sup>/day intravenously during late gestation and lactation showed signs of delayed development. It is not known whether docetaxel is excreted in human milk. It is recommended to advise women not to breastfeed during treatment with docetaxel and for 1 week after the last dose.

### 4.7 Effects on ability to drive and use machines

No studies of the effect on the ability to drive and use machines have been performed. Patients should refrain from driving or using machines until they know that the docetaxel does not negatively affect these abilities.

The amount of ethanol in docetaxel may impair the ability to drive or use machines. The alcohol content in a maximum recommended dose of 200mg (based on 100mg/m<sup>2</sup>, body surface area 2.0 m<sup>2</sup>) contains approximately 1.8 grams of absolute ethanol.

### 4.8 Undesirable effects

## Clinical Studies

### *Monotherapy*

#### Breast, non-small cell lung and ovarian cancer

The adverse effects considered to be possibly or probably related to starting the administration of docetaxel have been obtained from 75 patients who received a dose of 75 mg/m<sup>2</sup> without the recommended premedication and from 2,106 (2,045 with normal\* and 61 with elevated\* LFTs at baseline) patients who received an initially planned dose of 100 mg/m<sup>2</sup> over a one-hour infusion every three weeks independently of the premedication. The patients were enrolled in 40 phase II and III studies conducted in Europe and North America (991 with breast carcinoma, 668 with non-small cell lung carcinoma and 447 with various tumor types).

The safety profile is generally similar between patients receiving docetaxel for the treatment of breast, non-small cell lung or ovarian carcinoma. Table 2 lists the adverse effect data.

**Table 2: Summary of adverse events in patients receiving docetaxel at 75 and 100 mg/m<sup>2</sup> as a single agent**

Docetaxel dosage	Normal LFTs* at Baseline		Elevated LFTs* at Baseline
	75 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
Number of patients	n=75 %	n=2045 %	n=61 %
Hematological Toxicity			
Neutropenia ANC** < 2.0 cells x 10 <sup>9</sup> /L ANC** < 0.5 cells x 10 <sup>9</sup> /L	- 73.0	95.5 75.4	96.4 87.5
Febrile neutropenia (fever/ ANC** < 0.5 cells x 10 <sup>9</sup> /L)			

	Normal LFTs* at Baseline		Elevated LFTs* at Baseline
Docetaxel dosage	75 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
Number of patients	n=75 %	n=2045 %	n=61 %
by patient	-	11.0	26.2
by cycle	-	2.6*	8.7
(fever/ ANC** < 1 x 10 <sup>9</sup> /L)			
by patient	5.0	-	-
by cycle	1.5	-	-
Thrombocytopenia < 100 cells x 10 <sup>9</sup> /L	6.7	8.0	24.6
Anemia			
< 110 g/L	86.7	90.4	91.8
< 80 g/L	9.0	8.8	31.1
Non-Hematological Toxicity			
Body as a whole			
Fluid retention			
Regardless of premedication			
All	61.0	47.0	39.3
Severe	9.3	6.9	8.2
3-day premedication		[n=92]	[n=3]
All	-	64.1	66.7
Severe	-	6.5	33.3
Infections			
Overall	20.0	21.6*	32.8
Severe	1.3	6.1*	16.4
Asthenia			
All	56.0	61.8	52.5
Severe	5.0	12.8	24.6
Myalgia	10.7	18.9	16.4
Arthralgia	0.0	9.2	6.6
Neurological			
Neurosensory			
All	37.0	49.3	34.4
Severe	1.3	4.3	0.0
Neuromotor			
All	4.0	13.8	6.6
Severe	0.0	3.6	1.6
Cutaneous			
Skin			
All	45.3	47.6	54.1
Severe	1.3	4.8	9.8
Nail disorders	50.0	30.6	23.0
Alopecia	92.0	75.8	62.3

	Normal LFTs* at Baseline		Elevated LFTs* at Baseline
Docetaxel dosage	75 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>
Number of patients	n=75 %	n=2045 %	n=61 %
Gastrointestinal			
Nausea	44.0	38.9	37.7
Diarrhea	28.0	38.7	32.8
Vomiting	21.0	22.3	23.0
Stomatitis			
All	10.7	41.7	49.2
Severe	2.6	5.5	13.0
Mucositis	40.0	-	-
<b>Infusion site reactions</b> consisting of hyperpigmentation, inflammation, redness or dryness of skin, phlebitis or extravasation and swelling of the vein	5.6	4.4	3.3

\* Normal liver function tests (LFTs): transaminase  $\leq 1.5$  times upper limit of normal or alkaline phosphatase  $\leq 2.5$  times upper limit of normal or isolated elevations of transaminase or alkaline phosphatase up to five times upper limit of normal. \*\*ANC – absolute neutrophil count.

35 toxic deaths (1.7%) were reported in the 2,045 patients with normal baseline liver function tests treated with docetaxel as monotherapy at the initially planned dose of 100 mg/m<sup>2</sup>. Septic deaths (neutropenic infections, pneumonia or sepsis) accounted for 80% of the toxic deaths. The incidence of toxic deaths was higher (9.8%) in patients with elevated baseline LFTs.

Hypersensitivity reactions generally occurred within a few minutes of the start of infusion and were generally mild to moderate. Frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnea and drug fever or chills (see **Section 4.4 Special warnings and precautions for use**).

#### *Hematological*

Bone marrow suppression and other hematological adverse reactions to docetaxel include the following:

Neutropenia (in patients who did not receive G-CSF), the most frequent adverse effect, was reversible and not cumulative. The median day to nadir was seven days and the median duration of severe neutropenia was seven days.

Febrile neutropenia and severe infections associated with neutrophil counts  $< 0.5 \times 10^9/L$ , infectious episodes (severe including sepsis pneumonia, fatal in 1.7%), occurred. Thrombocytopenia, bleeding episodes (rarely associated with severe thrombocytopenia) and anemia (severe) were also reported.

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

#### *Neurological*

Mild to moderate neurosensory signs and/or symptoms occurred in 50% of the patients. Severe neurosensory symptoms (paresthesia, dysesthesia, pain including burning) were observed in 4.1% of metastatic breast cancer patients and resulted in treatment discontinuation in 2%.

Neuro-motor events (13.8% with 4% severe) were mainly characterized by weakness. 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 were available had spontaneous reversal of symptoms with a median of 81 days from onset (range 0 to 741 days).

Rare cases of convulsion or transient loss of consciousness have been observed with docetaxel administration. These reactions sometimes appear during the infusion of the drug.

### *Hepatic*

In patients treated at 100 mg/m<sup>2</sup> as a single agent, increase in serum levels of AST, ALT, bilirubin and alkaline phosphatase greater than 2.5 the ULN were observed in less than 5% of patients. Very rare cases of hepatitis have been reported.

## **Combination Therapy**

### Breast cancer

#### *Metastatic breast cancer*

#### Combination with Capecitabine

The adverse effect profile is consistent with the known toxicities of monotherapy treatments. The most frequent treatment related adverse effects (greater than or equal to 5%) reported in the phase III clinical trial for docetaxel in combination with capecitabine in patients with locally advanced and/or metastatic breast cancer (n = 251) are shown in Table 3.

The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (20%) in the monotherapy arm discontinued from the trial because of adverse effects. The percentages of patients requiring dose reductions due to adverse effects were 65% in the combination arm and 36% in the monotherapy arm.

**Table 3: Treatment related adverse effects reported in ≥ 5% of patients treated with docetaxel in combination with capecitabine**

Body system Adverse event	Capecitabine 1250 mg/m <sup>2</sup> twice daily with docetaxel 75 mg/m <sup>2</sup> /3 weeks (n=251)		Docetaxel 100mg/m <sup>2</sup> /3 weeks (n=255)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
<b>Gastrointestinal</b>				
Stomatitis	67	18	42	5
Diarrhea	64	14	45	5
Nausea	43	6	35	2
Vomiting	33	4	22	1
Constipation	14	1	12	-
Abdominal pain	14	2	9	1
Dyspepsia	12	-	5	<1
Abdominal pain upper	9	-	6	1
Dry mouth	5	-	4	-

Body system Adverse event	Capecitabine 1250 mg/m <sup>2</sup> twice daily with docetaxel 75 mg/m <sup>2</sup> /3 weeks (n=251)		Docetaxel 100mg/m <sup>2</sup> /3 weeks (n=255)	
	All Grades %	Grade <sup>3</sup> / <sub>4</sub> %	All Grades %	Grade <sup>3</sup> / <sub>4</sub> %
<b>Cutaneous</b>				
Hand-foot syndrome	63	24	7	1
Alopecia	41	6	42	7
Nail disorder	14	2	15	-
Dermatitis	8	-	9	1
Rash erythematous	8	<1	4	-
Nail discoloration	6	-	4	<1
Onycholysis	5	1	5	1
<b>General</b>				
Asthenia	23	3	22	5
Pyrexia	21	1	29	<1
Fatigue	21	4	25	5
Weakness	13	1	9	2
Pain in limb	9	<1	8	<1
Lethargy	6	-	5	1
Pain	6	-	2	-
<b>Neurologic</b>				
Taste disturbance	15	<1	14	<1
Paresthesia	11	<1	15	1
Dizziness	9	-	6	<1
Headache	7	<1	8	1
Peripheral neuropathy	5	-	10	1
<b>Cardiovascular</b>				
Lower limb edema	14	1	12	1
Sore throat	11	2	7	<1
Dyspnea	7	1	9	<1
Cough	6	<1	9	-
Epistaxis	5	<1	5	-
<b>Metabolism</b>				
Anorexia	12	1	10	1
Decreased appetite	10	-	4	-
Dehydration	8	2	5	1
Decreased weight	6	-	4	-
<b>Eye</b>				
Increased lacrimation	12	-	5	-
<b>Musculoskeletal</b>				
Myalgia	14	2	24	2
Arthralgia	11	1	18	2
Back pain	7	1	6	1
<b>Infection</b>				
Oral candidiasis	6	<1	7	<1

Body system Adverse event	Capecitabine 1250 mg/m <sup>2</sup> twice daily with docetaxel 75 mg/m <sup>2</sup> /3 weeks (n=251)		Docetaxel 100mg/m <sup>2</sup> /3 weeks (n=255)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
<b>Hematological*</b>				
Decreased hemoglobin	13	4	11	4
Neutropenic fever	21	16	21	21
Leukopenia	3	3	2	2
<b>Biochemical laboratory abnormalities*</b>				
Increased alkaline phosphatase	51	1	48	2
Increased bilirubin	23	9	6	3
Increased AST	42	3	37	4
Increased ALT	30	2	30	2
Serum creatinine	7	<1	4	-

\* Grades according to National Cancer Institute of Canada Toxicity Criteria, version 1, Dec 1994 were used

Frequent grade 3 and 4 laboratory abnormalities are shown in Table 4.

**Table 4: Frequent grade 3 and 4 laboratory abnormalities were:**

Adverse Event	capecitabine with docetaxel (n=251)
Laboratory abnormalities	Grade 3/4
	%
Neutropenia	63
Anemia	10
Thrombocytopenia	3
Hyperbilirubinemia	9

Rare or uncommon adverse effects, as described for capecitabine monotherapy, can be expected for combination therapy as well. See capecitabine Product Information for adverse effects which are at least remotely related to capecitabine occurring in < 5% of patients treated with capecitabine in combination with docetaxel.

Combination with trastuzumab (HER2+)

See Table 5.

**Table 5: Adverse events (all grades) which were reported in  $\geq 10\%$  of patients treated with docetaxel in combination with trastuzumab for metastatic breast cancer**

Body System	Adverse Event	docetaxel plus trastuzumab N=92 (%)
General disorders and administration site conditions	Asthenia	45
	Pyrexia	30
	Fatigue	24
	Mucosal inflammation	24
	Rigors	11
	Pain	11
	Chest pain	10
	Influenza like illness	10
	Lethargy	7
Skin and subcutaneous tissue disorders	Alopecia	67
	Rash	24
	Erythema	23
	Nail disorder	16
Fluid retention	Peripheral	40
	Weight increased	16
	Lymphedema	11
Gastrointestinal disorders	Nausea	45
	Diarrhea	43
	Vomiting	29
	Constipation	27
	Stomatitis	20
	Dyspepsia	14
	Abdominal pain	12
Nervous system disorders	Paresthesia	32
	Headache	21
	Dysgeusia	14
	Hypoesthesia	11
Blood and lymphatic system disorders	Neutropenia	33
	Febrile neutropenia	20
	Anemia	15
	Leukopenia	12
Musculoskeletal and connective tissue disorders	Myalgia	27
	Arthralgia	27
	Pain in extremity	16
	Bone pain	14
	Back pain	11
Respiratory, thoracic and mediastinal disorders	Epistaxis	20
	Pharyngolaryngeal pain	16
	Nasopharyngitis	15
	Dyspnea	14
	Cough	13
	Rhinorrhea	12
	Lacrimation increased	21
	Conjunctivitis	12
Metabolism and nutrition disorders	Anorexia	22
Psychiatric disorders	Insomnia	12
Injury, poisoning and procedural complications	Nail toxicity	11

There was an increased incidence of SAEs (40% vs. 31%) and grade 4 AEs (34% vs. 23%) in the combination arm compared to docetaxel monotherapy.

#### *Cardiac toxicity*

The incidence of symptomatic congestive heart failure in the study of docetaxel plus trastuzumab versus docetaxel alone is shown in Table 6.

**Table 6: Overview of cardiac adverse event incidence (n,%) [95% confidence limits]**

	<b>docetaxel plus trastuzumab n=92</b>	<b>docetaxel n=94</b>
Symptomatic heart failure	2 (2.2%)	0%

In this study, all patients had a baseline cardiac ejection fraction of greater than 50%. In the docetaxel plus trastuzumab arm, 64% had received a prior anthracycline as adjuvant therapy, compared with 55% in the docetaxel alone arm.

#### *Hematological toxicity*

Grade 3/4 neutropenia was reported in 32% of the patients given docetaxel plus trastuzumab.

### ***Adjuvant Treatment of Breast Cancer***

#### Combination with doxorubicin and cyclophosphamide

Table 7 presents clinically important treatment emergent adverse events (TEAEs) observed in 744 patients, who were treated with docetaxel 75 mg/m<sup>2</sup> every three weeks in combination with doxorubicin and cyclophosphamide and 736 patients, treated with the comparator study drugs.

**Table 7: Clinically important treatment emergent adverse events (TEAEs) considered related to study treatment in patients receiving docetaxel in combination with doxorubicin and cyclophosphamide**

Body system Adverse Event	<b>Docetaxel 75 mg/m<sup>2</sup> + doxorubicin 50 mg/m<sup>2</sup> + cyclophosphamide 500 g/m<sup>2</sup> n=744</b>		<b>Fluorouracil 500 mg/m<sup>2</sup> + doxorubicin 50 mg/m<sup>2</sup> + cyclophosphamide 500 g/m<sup>2</sup> n=736</b>	
	<b>Any %</b>	<b>Grade 3/4 %</b>	<b>Any %</b>	<b>Grade 3/4 %</b>
<b>Cutaneous</b>				
Alopecia	97.7	N/A	97.1	N/A
Skin toxicity	18.4	0.7	10.9	0.3
Nail disorders	18.4	0.4	13.9	0.1
<b>Hematological</b>				
Anemia	91.5	4.3	71.7	1.6
Neutropenia	71.4	65.5	82.0	49.3
Thrombocytopenia	39.4	2.0	27.7	1.2
Febrile neutropenia	24.7	N/A	2.5	N/A
Neutropenic infection	12.1	N/A	6.3	N/A

Body system Adverse Event	Docetaxel 75 mg/m <sup>2</sup> + doxorubicin 50 mg/m <sup>2</sup> + cyclophosphamide 500 g/m <sup>2</sup> n=744		Fluorouracil 500 mg/m <sup>2</sup> + doxorubicin 50 mg/m <sup>2</sup> + cyclophosphamide 500 g/m <sup>2</sup> n=736	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %
<b>Gastrointestinal</b>				
Nausea	80.4	5.1	87.4	9.5
Stomatitis	69.1	7.1	52.6	2.0
Vomiting	42.6	4.3	58.2	7.3
Diarrhea	30.9	3.2	23.5	1.0
Constipation	22.6	0.4	21.5	1.2
Abdominal pain	7.3	0.5	3.3	0.0
<b>General</b>				
Asthenia	79.2	11.0	69.4	5.2
Fever in absence of infection	43.1	1.2	13.2	0.0
Infection*	27.2	3.2	17.4	1.4
Peripheral edema	26.7	0.4	7.2	0.0
Hypersensitivity reactions	10.5	1.1	2.2	0.0
Lymphedema	0.3	0.0	0.0	0.0
<b>Gynecological</b>				
Amenorrhea	57.6	N/A	48.1	N/A
<b>Neurological</b>				
Taste perversion	27.4	0.7	15.1	0.0
Neuropathy sensory	23.8	0.0	7.9	0.0
Neuro-cortical	2.8	0.3	3.9	0.3
Neuropathy motor	2.8	0.0	1.5	0.0
Neuro-cerebellar	1.1	0.1	0.8	0.0
Syncope	0.5	0.0	0.4	0.0
<b>Musculoskeletal</b>				
Myalgia	22.8	0.8	8.0	0.0
Arthralgia	15.1	0.4	5.7	0.3
<b>Cardiovascular</b>				
CHF	0.0	1.6	0.0	0.5
Vasodilatation	20.3	0.9	15.9	0.4
Cardiac dysrhythmias**	3.9	0.1	2.9	0.3
Hypotension	1.5	0.0	0.5	0.0
Phlebitis	0.7	0.0	0.4	0.0
<b>Metabolic</b>				
Anorexia	19.9	2.2	16.4	1.2
Weight gain or loss	15.2	0.3	9.2	0.0
<b>Eye</b>				
Lacrimation disorder	9.8	0.1	6.4	0.0
Conjunctivitis	4.6	0.3	6.0	0.1
<b>Respiratory</b>				
Cough	3.1	0.0	2.2	0.1

N/A: not applicable. \*There was no septic death in either treatment arms. \*\*one patient died due to heart failure in TAC arm.

Of the 744 patients treated with TAC (docetaxel, doxorubicin and cyclophosphamide), 33.1% experienced severe TEAEs. Dose reductions due to hematological toxicity occurred in 1% of cycles in TAC arm. 6% of patients treated with TAC discontinued treatment due to adverse events, fever in the absence of infection and allergy being the most common reasons for withdrawal. Two patients died within 30 days of their last study treatment; 1 death was considered to be related to study drug.

#### *Fever and infection*

Fever in the absence of infection was seen in patients and infection was seen in patients. There were no septic deaths.

#### *Gastrointestinal events*

In addition to gastrointestinal events reflected in Table 7, four patients were reported to have colitis/ enteritis/ large intestine perforation in the TAC arm. Two of these patients required treatment discontinuation; no deaths due to these events occurred during the treatment period.

#### *Acute myeloid leukemia/ myelodysplastic syndrome*

At a median follow-up time of 83 months, AML occurred in three of 744 (0.4%) patients who received docetaxel, doxorubicin and cyclophosphamide and in one of 736 (0.1%) patients who receive fluorouracil, doxorubicin and cyclophosphamide.

#### *Cardiovascular events*

The following cardiovascular events were reported: dysrhythmias, all grades (3.9%), hypotension, all grades (1.5%) and CHF (2.3% at 70 months median follow-up). One patient died due to heart failure.

#### *Other persistent reactions*

The following events were observed to be ongoing at the median follow-up time of 55 months: alopecia, amenorrhea, neurosensory and peripheral edema. Among the adverse events that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhea, and lymphedema remained ongoing in TAC patients.

#### Combination with doxorubicin, cyclophosphamide and trastuzumab and with carboplatin and trastuzumab (HER2+).

See Table 8.

**Table 8: Adverse events (AEs) related to study treatment, occurring at any time during the study: safety population (incidence of  $\geq 5\%$  for noncardiac AEs: incidence of  $\geq 1\%$  for cardiac AEs)**

Adverse Event (NCI-CTC term)	AC-T n=1050		AC-TH n=1068		TCH n=1056	
	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)
Alopecia	1029 (98.0)	0	1047 (98.0)	0	1012 (95.8)	0
Hemoglobin <sup>a</sup>	957(91.1)	25 (2.4)	1036 (97.0)	34 (3.2)	1017 (96.3)	61(5.8)
Nausea	916 (87.2)	61(5.8)	931 (87.2)	57 (5.3)	853 (80.8)	49(4.6)
Leukocytes <sup>a</sup>	878 (83.6)	540 (51.4)	929 (87.0)	643 (60.2)	877 (83.0)	507 (48.0)
Neutrophils <sup>a</sup>	859 (81.8)	664 (63.2)	922 (86.3)	761 (71.3)	859 (81.3)	696 (65.9)

Adverse Event (NCI-CTC term)	AC-T n=1050		AC-TH n=1068		TCH n=1056	
	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)
Fatigue	844 (80.4)	71 (6.8)	868 (81.3)	71 (6.6)	849 (80.4)	73 (6.9)
Stomatitis/pharyngitis	663 (63.1)	38(3.6)	694 (65.0)	32 (3.0)	547 (51.8)	15 (1.4)
Vomiting	571 (54.4)	61 (5.8)	591 (55.3)	68 (6.4)	416 (39.4)	32 (3.0)
SGPT (ALT) <sup>a</sup>	506 (48.2)	7 (0.7)	579 (54.2)	19 (1.8)	561 (53.1)	25 (2.4)
Fluid retention <sup>a,b</sup>	533 (50.8)	14 (1.3)	558 (52.2)	16 (1.5)	539 (51.0)	15 (1.4)
Myalgia	515 (49.0)	49 (4.7)	544 (50.9)	52 (4.9)	353 (33.4)	15 (1.4)
Diarrhea	395 (37.6)	31 (3.0)	484 (45.3)	55 (5.1)	589 (55.8)	52 (4.9)
Neuropathy-sensory	464 (44.2)	23 (2.2)	478 (44.8)	20 (1.9)	316 (29.9)	6(0.6)
SGOT (AST) <sup>a</sup>	426 (40.6)	2 (0.2)	454(42.5)	9 (0.8)	401 (38.0)	11(1.0)
Arthralgia	372 (35.4)	30 (2.9)	424 (39.7)	32 (3.0)	230 (21.8)	11(1.0)
Nail changes	487 (46.4)	0	423 (39.6)	0	246 (23.3)	0
Platelets <sup>a</sup>	296 (28.2)	10 (1.0)	350 (32.8)	13 (1.2)	667 (63.2)	57 (5.4)
Irregular menses	353 (33.6)	248 (23.6)	311 (29.1)	213 (19.9)	340 (32.2)	226 (21.4)
Taste disturbance	297 (28.3)	0	290 (27.2)	0	312 (29.5)	0
Constipation	276 (26.3)	6 (0.6)	289 (27.1)	10 (0.9)	232 (22.0)	6 (0.6)
Rash/desquamation	224 (21.3)	16(1.5)	277(25.9)	14(1.3)	241(22.8)	4(0.4)
Hot flashes/flushes	220 (21.0)	0	230 (21.5)	0	192 (18.2)	0
Tearing	191 (18.2)	0	228 (21.3)	3 (0.3)	109 (10.3)	0
Alkaline phosphatase <sup>a</sup>	202 (19.2)	3 (0.3)	206 (19.3)	3 (0.3)	215 (20.4)	3 (0.3)
Anorexia	214 (20.4)	5 (0.5)	205 (19.2)	5 (0.5)	222 (21.0)	5 (0.5)
Dyspepsia/heartburn	150 (14.3)	3 (0.3)	203 (19.0)	3 (0.3)	211 (20.0)	4 (0.4)
Headache	163 (15.5)	4 (0.4)	175 (16.4)	6 (0.6)	160 (15.2)	3 (0.3)
Dyspnea	156 (14.9)	8 (0.8)	166 (15.5)	16 (1.5)	157 (14.9)	18 (1.7)
Weight gain	114 (10.9)	3 (0.3)	159 (14.9)	3 (0.3)	154 (14.6)	2 (0.2)
Infection without neutropenia	105 (10.0)	17 (1.6)	135 (12.6)	20 (1.9)	98 (9.3)	16 (1.5)
Abdominal pain or cramping	108 (10.3)	3 (0.3)	132 (12.4)	4 (0.4)	141 (13.4)	5 (0.5)
Insomnia	106 (10.1)	0	119 (11.1)	1 (0.1)	93 (8.8)	0
Febrile neutropenia	95 (9.0)	95 (9.0)	116 (10.9)	116 (10.9)	103 (9.8)	103 (9.8)
Fever (without neutropenia)	95 (9.0)	3 (0.3)	116 (10.9)	4 (0.4)	70 (6.6)	3 (0.3)
Allergic reaction / hypersensitivity	75 (7.1)	12 (1.1)	105 (9.8)	15 (1.4)	139 (13.2)	26 (2.5)
Bone pain	97 (9.2)	10 (1.0)	104 (9.7)	4 (0.4)	67 (6.3)	1 (0.1)
Infection with grade 3/4 neutropenia	83 (7.9)	83 (7.9)	98 (9.2)	98 (9.2)	81 (7.7)	81 (7.7)
Pain	98 (9.3)	4 (0.4)	86 (8.1)	4 (0.4)	57 (5.4)	0
Conjunctivitis	84 (8.0)	5 (0.5)	86 (8.1)	0	35 (3.3)	0
Dizziness/lightheadedness	65 (6.2)	1 (0.1)	78 (7.3)	7 (0.7)	70 (6.6)	4 (0.4)
Creatinine <sup>a</sup>	39 (3.7)	7 (0.7)	72 (6.7)	5 (0.5)	102 (9.7)	6 (0.6)
Hand-foot skin reaction	84 (8.0)	20 (1.9)	72 (6.7)	15 (1.4)	29 (2.7)	0
Epistaxis	40 (3.8)	0	72 (6.7)	0	104 (9.8)	4 (0.4)
Weight loss	63 (6.0)	0	71 (6.6)	0	56 (5.3)	1 (0.1)
Dry skin	63 (6.0)	0	69 (6.5)	0	41 (3.9)	0
Cough	55 (5.2)	1 (0.1)	66 (6.2)	2 (0.2)	36 (3.4)	0
Rhinitis	49 (4.7)	2 (0.2)	64 (6.0)	1 (0.1)	47 (4.5)	0
Rigors, chills	33 (3.1)	0	63 (5.9)	0	54 (5.1)	0
Infection with unknown ANC	73 (7.0)	73 (7.0)	59 (5.5)	59 (5.5)	38 (3.6)	38 (3.6)
Neuropathy-motor	44 (4.2)	2 (0.2)	57 (5.3)	4 (0.4)	38 (3.6)	3 (0.3)
Bilirubin <sup>a</sup>	52 (5.0)	6 (0.6)	54 (5.1)	4 (0.4)	61 (5.8)	4 (0.4)
Injection site reaction	47 (4.5)	2 (0.2)	50 (4.7)	1 (0.1)	61 (5.8)	2 (0.2)
Mouth dryness	76 (7.2)	0	43 (4.0)	0	29 (2.7)	0
Cardiac left ventricular function	11 (1.0)	1 (0.1)	37 (3.5)	5 (0.5)	15 (1.4)	1 (0.1)

Adverse Event (NCI-CTC term)	AC-T n=1050		AC-TH n=1068		TCH n=1056	
	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)
Palpitations	32 (3.0)	0	36 (3.4)	0	47 (4.5)	0
Sinus tachycardia	21 (2.0)	2 (0.2)	19 (1.8)	0	23 (2.2)	0
Hypotension	10 (1.0)	1 (0.1)	10 (0.9)	0	13 (1.2)	2 (0.2)

ACT = doxorubicin, cyclophosphamide and docetaxel; AC-TH = doxorubicin and cyclophosphamide, followed by docetaxel in combination with trastuzumab; TCH = docetaxel in combination with trastuzumab and carboplatin. <sup>a</sup>Regardless of causality. <sup>b</sup>Fluid retention AEs are defined as ‘edema only’, or ‘weight gain only’, or ‘lung edema only’, or ‘edema and weight gain’, or ‘edema and lung edema’ or ‘edema+weight gain+lung edema’. ‘Fluid retention’ corresponds to the NCI-CTC term ‘edema’.

The 3-year cumulative incidence of all symptomatic cardiac events was 2.36% and 1.16% in the AC-TH and TCH arms, respectively (versus 0.52% in the AC-T control arm, see **Section 5.1 Pharmacodynamic properties**). The 3-year cumulative incidence of CHF events (Grade 3 or 4) was 1.9% and 0.4% in the AC-TH and TCH arms, respectively (versus 0.3% in the AC-T control arm).

#### Combination with Cyclophosphamide (TC)

Whilst overall the toxicity profiles were similar, there were some differences between TC and AC (doxorubicin and cyclophosphamide). AC was associated with more nausea and vomiting (all grades as well as grades 3 and 4), but TC had more low-grade edema, myalgia, and arthralgia secondary to the use of docetaxel. The exception was cardiac toxicity. In the AC arm one patient died of congestive heart failure and there were four deaths due to myocardial infarction. At the 7-year follow up another death in the AC arm was attributed to congestive heart failure. In the TC arm there were no deaths attributed to congestive heart failure and two deaths from myocardial infarction.

**Table 9: Tabulated frequency of the most common adverse events**

	TC Patients (n=506)				AC Patients (n=510)			
	Grade (%)				Grade (%)			
Adverse Event	1	2	3	4	1	2	3	4
<b>Hematologic</b>								
Anemia	3	2	<1	<1	4	3	1	<1
Neutropenia	<1	1	10	51	1	2	12	43
Thrombocytopenia	<1	<1	0	<1	<1	<1	1	0
<b>Non-hematologic</b>								
Asthenia	43	32	3	<1	42	31	4	<1
Edema	27	7	<1	0	17	3	<1	<1
Fever	14	5	3	2	11	4	2	<1
Infection	8	4	7	<1	7	5	8	<1
Myalgia	22	10	1	<1	11	5	<1	<1
Nausea	38	13	2	<1	43	32	7	<1
Phlebitis	8	3	<1	0	1	1	0	0
Stomatitis	23	10	<1	<1	29	15	1	1
Vomiting	9	5	<1	<1	21	16	5	<1

AC – doxorubicin and cyclophosphamide; TC – docetaxel and cyclophosphamide

#### ***Prostate cancer***

#### Combination with prednisone (or prednisolone)

The adverse effect profile is consistent with the known safety profile of docetaxel. Table 10 provides the percentage of subjects with clinically important TEAs and hematological toxicities related to study treatment reported in the phase III clinical trial for docetaxel 75 mg/m<sup>2</sup> q3w (every three weeks) and mitozantrone q3w in combination with prednisone (or prednisolone).

**Table 10: Clinically important treatment emergent adverse events related to study medication**

	Docetaxel 75 mg/m <sup>2</sup> every 3 weeks (n=332) %		Mitozantrone 12 mg/ m <sup>2</sup> every 3 weeks (n=335) %	
	Grade 3/4	Any	Grade 3/4	Any
<b>Cutaneous</b>				
Alopecia	N/A *	65.1	N/A *	12.5
Nail changes	0.0	28.3	0.0	6.6
Rash/desquamation	0.3	3.3	0.0	0.9
<b>Hematological</b>				
Neutropenia	32.0	40.9	21.7	48.2
Anemia	4.9	66.5	1.8	57.8
Thrombocytopenia	0.6	3.4	1.2	7.8
Epistaxis	0.0	3.0	0.0	0.6
Febrile neutropenia	N/A *	2.7	N/A *	1.8
<b>General</b>				
Fatigue	3.9	42.8	2.7	26.6
Infection	3.3	12.0	2.1	4.8
Stomatitis/pharyngitis	0.9	17.8	0.0	7.8
Fluid retention	0.6	24.4	0.3	4.5
Allergic reaction	0.6	6.9	0.0	0.3
Anorexia	0.6	12.7	0.0	11.6
<b>Gastrointestinal</b>				
Nausea	2.4	35.5	0.9	28.7
Diarrhea	1.2	24.1	0.9	4.2
Vomiting	1.2	13.3	0.6	7.2
<b>Neurological</b>				
Neuropathy sensory	1.2	27.4	0.0	2.1
Taste disturbance	0.0	17.5	0.0	6.3
Neuropathy motor	0.0	3.9	0.0	0.9
<b>Respiratory</b>				
Dyspnea	0.6	4.5	0.3	3.3
Cough	0.0	1.2	0.0	0.9
<b>Eye</b>				
Tearing	0.6	9.3	0.0	1.5
<b>Musculoskeletal</b>				
Myalgia	0.3	6.9	0.0	3.3
Arthralgia	0.3	3.0	0.0	0.6

	Docetaxel 75 mg/m <sup>2</sup> every 3 weeks (n=332) %		Mitozantrone 12 mg/ m <sup>2</sup> every 3 weeks (n=335) %	
	Grade 3/4	Any	Grade 3/4	Any
<b>Cardiovascular</b> Abnormal cardiac left ventricular function	0.3	3.9	0.9	19.1

\* N/A: not applicable

### ***Head and neck cancer***

#### Combination with cisplatin and fluorouracil

Table 11 summarizes the safety data obtained in 174 (TAX323) and 251 patients (TAX 324) with locally advanced SCCHN who were treated with docetaxel 75 mg/m<sup>2</sup> in combination with cisplatin and fluorouracil.

**Table 11: Clinically important treatment related adverse events in patients with SCCHN receiving docetaxel in combination with cisplatin and fluorouracil**

Adverse Event	TAX 323: docetaxel 75mg/m <sup>2</sup> + cisplatin 75mg/m <sup>2</sup> + fluorouracil 750 mg/m <sup>2</sup> (n=174)		TAX 324: docetaxel 75mg/m <sup>2</sup> + cisplatin 100mg/m <sup>2</sup> + fluorouracil 1000 mg/m <sup>2</sup> (n=251)	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %
<b>Blood and lymphatic system</b>				
Neutropenia	93.1	76.3	94.8	83.5
Anemia	89.1	9.2	90.0	12.4
Thrombocytopenia	23.6	5.2	27.5	4.0
Infection	15.5	6.3	13.1	3.6
Fever in absence of infection	14.4	0.6	26.3	3.6
Neutropenic infection	11.0	0.0	6.5	NA
Febrile neutropenia*	5.2	0.0	12.1	NA
<b>Allergy</b>	2.9	0.0	0.4	0.0
<b>Skin and subcutaneous tissue disorders</b>				
Alopecia	79.9	10.9	67.7	4.0
Rash/itch	8.6	0.0	12.7	0.0
Dry skin	5.2	0.0	2.8	0.4
Desquamation	4.0	0.6	2.0	0.0
<b>Fluid retention</b>	20.1	0.0	13.1	1.2
Edema only	12.6	0.0	12.0	1.2
Weight gain only	5.7	0.0	0.4	0.0

Adverse Event	TAX 323: docetaxel 75mg/m <sup>2</sup> + cisplatin 75mg/m <sup>2</sup> + fluorouracil 750 mg/m <sup>2</sup> (n=174)		TAX 324: docetaxel 75mg/m <sup>2</sup> + cisplatin 100mg/m <sup>2</sup> + fluorouracil 1000 mg/m <sup>2</sup> (n=251)	
	Any %	Grade 3/4 %	Any %	Grade 3/4 %
<b>Gastrointestinal disorders</b>				
Nausea	43.7	0.6	75.7	13.9
Stomatitis	42.0	4.0	64.5	20.7
Diarrhea	29.3	2.9	42.2	6.8
Vomiting	25.9	0.6	56.2	8.4
Taste/sense of smell altered	10.3	-	19.5	0.4
Constipation	6.9	0.0	13.9	0.4
Esophagitis/dysphagia/odynophagia	5.7	0.6	21.9	12.0
Gastrointestinal pain/cramping	5.2	-	6.0	1.2
Heartburn	4.0	-	8.8	0.8
Gastrointestinal bleeding	1.1	0.6	2.0	0.4
<b>Nervous system disorders</b>				
Neurosensory	16.7	0.6	11.6	1.2
Neuromotor	-	-	7.2	0.4
Dizziness	1.1	-	9.6	2.0
<b>Cardiac disorders</b>				
Myocardial ischemia	1.7	1.7	0.8	0.8
Cardiac dysrhythmia	0.6	0.6	3.2	0.2
<b>Vascular disorders</b>				
Venous	1.1	0.6	0.8	0.4
<b>Metabolism and nutrition disorders</b>				
Anorexia	15.5	0.6	37.8	12.0
Weight loss	9.8	0	11.2	0.0
<b>Eye disorders</b>				
Tearing	1.7	0	1.6	0.0
Conjunctivitis	1.1	0	0.8	0.0
<b>Ear and labyrinth disorders</b>				
Altered hearing	5.7	0	11.2	1.2
<b>Musculoskeletal, connective tissue and bone disorders</b>				
Myalgia	6.3	0.6	5.2	0.4
<b>General disorders and administration site conditions</b>				
Lethargy	37.9	3.4	58.6	4.0
Cancer pain	1.1	0.6	3.2	1.2

\* Febrile neutropenia: grade  $\geq 2$  fever concomitant with Grad 4 neutropenia requiring I.V antibiotics and/or hospitalization. Clinically important TEAEs were determined based upon frequency, severity and clinical impact of the adverse event.

## Post-marketing Adverse Effects

The following information relates to serious events observed following the marketing of docetaxel. Voluntary reports of serious adverse events that have been received since market introduction (without causal relationship) that are not listed previously are cited below. Frequency estimates are as follows. Common: greater than or equal to 1 to 10%; uncommon: 0.1 to 1%; rare: 0.01 to 0.1%; very rare: < 0.01%.

### ***Body as a whole***

Uncommon: chest pain, diffuse pain.

Rare: abdominal pain.

Very rare: radiation recall phenomenon.

### ***Hypersensitivity***

Rare: cases of anaphylactic shock have been reported.

Very rare: these cases resulted in a fatal outcome in patients who received premedication.

Hypersensitivity reactions such as bronchospasm and generalized rash have been reported.

Hypersensitivity reactions have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

### ***Cutaneous***

Very rare: cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes have been reported. Multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects. Cases of permanent alopecia have been reported.

Severe nail disorders characterized by hypo or hyperpigmentation, and infrequently onycholysis and pain.

Acute generalized exanthematous pustulosis has been reported.

### ***Fluid retention***

Rare: dehydration and pulmonary edema have been reported.

### ***Gastrointestinal***

Rare: constipation, esophagitis and taste perversion, ileus and intestinal obstruction, gastrointestinal perforation, neutropenic enterocolitis<sup>a</sup>, colitis<sup>a</sup>, including ischemic colitis<sup>a</sup>, gastrointestinal hemorrhage, dehydration as a consequence of gastrointestinal events.

Very rare: duodenal ulcer.

<sup>a</sup> Reported with a fatal outcome

### ***Neurological***

Rare: confusion, seizures, transient loss of consciousness. These reactions sometimes occur during infusion of the drug.

### ***Cardiovascular***

Common: hypertension, hypotension.

Uncommon: cardiac arrhythmia<sup>b</sup>, congestive heart failure.

Rare: atrial fibrillation, syncope, tachycardia<sup>b</sup>.

Very rare: deep vein thrombosis, myocardial infarction, ECG abnormalities, thrombophlebitis, pulmonary embolism.

Vein disorder, venous thromboembolism and hemorrhage have been reported.

<sup>b</sup> In post-marketing, 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.

### ***Hepatic***

Very rare: hepatitis, sometimes fatal, primarily in patients with pre-existing liver disorders, has been reported.

### ***Ear and labyrinth disorders***

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

Hypoacusis has been recorded.

### ***Eye disorders***

Rare: cases of lacrimation with or without conjunctivitis have been reported and very rare cases of lacrimal duct obstruction resulting in excessive tearing have been reported primarily in patients receiving other antitumor agents concomitantly.

Cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity 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, as well as with other taxanes.

### ***Respiratory, thoracic and mediastinal disorders***

Uncommon: dyspnea.

Rare: acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, acute pulmonary edema, pulmonary fibrosis, and radiation recall phenomena have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant therapy.

Respiratory failure has been reported.

### ***Hematological and lymphatic disorders***

Very rare: cases of acute myeloid leukemia and myelodysplastic syndrome have been reported in association with docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.

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

### ***Urogenital***

Rare: renal insufficiency and renal failure associated with concomitant nephrotoxic drugs have been reported.

### ***Musculoskeletal and connective tissue disorders***

Myositis has been reported.

### ***Other***

Common: generalized or localized pain including chest pain without cardiac or respiratory involvement.

### ***Metabolism and nutrition disorders***

Tumor lysis syndrome has been reported. Cases of electrolyte imbalance have been reported. Cases of hyponatremia have been reported, mostly associated with dehydration, vomiting and pneumonia. Hypokalemia, hypomagnesemia and hypocalcemia were observed, usually in association with gastrointestinal disorders and in particular diarrhea.

### ***General disorders and administration site conditions***

Fluid retention (pleural effusion, pericardial effusion, ascites), injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) has been observed at the site of previous extravasation.

### ***Investigations***

Liver function test abnormal, weight decreased, blood bilirubin increased, blood alkaline phosphatase increased, AST increased, ALT increased.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

## **4.9 Overdose and treatment**

### **Symptoms**

There were two reports of overdose. One patient received docetaxel 150 mg/m<sup>2</sup> and the other received docetaxel 200 mg/m<sup>2</sup> as a one-hour infusion. They both recovered after experiencing severe neutropenia, mild asthenia, cutaneous reactions and mild paresthesia.

### **Treatment**

In case of overdosage, the patient should be kept in a specialized unit and vital functions closely monitored. Exacerbation of adverse events may be expected. There is no known antidote for docetaxel overdosage. The primary anticipated complications of overdosage would consist of 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.

## 5.0 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

#### Mechanism of action

Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions.

#### Class

Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

#### Clinical trials

##### ***Breast Cancer***

##### Metastatic Breast Cancer

##### *Monotherapy*

Eight phase II studies were conducted in patients with locally advanced or metastatic breast carcinoma. A total of 172 patients had received no prior chemotherapy (previously untreated) and 111 patients had received prior chemotherapy (previously treated) which included 83 patients who had progressive disease during anthracycline therapy (anthracycline resistant). In these clinical trials, docetaxel was administered at a dose of 75 mg/m<sup>2</sup> in 55 previously untreated patients and at a dose of 100 mg/m<sup>2</sup> in 117 previously untreated and 111 previously treated patients. In these trials, docetaxel was administered as a one-hour infusion every three weeks.

##### *Patients treated at 75 mg/m<sup>2</sup>*

In the intent to treat analysis on previously untreated patients, the overall response rate was 47% with 9% complete responses. The median duration of response was 34 weeks and the time to progression was 22 weeks.

There was a high response rate in patients with visceral metastases (48.6% in 35 untreated patients).

In patients with two or less organs involved, the response rate was 58.6% and in patients with three or more organs involved, it was 29.4%.

A significant response rate was seen in patients with liver metastases (45% in untreated patients). The same activity is maintained in untreated patients with soft tissue disease (55.5%).

##### *Patients treated at 100 mg/m<sup>2</sup>. Phase II trials*

In the intent to treat analysis on previously untreated patients, the overall response rate was 56% with 9.4% complete responses. The overall response rate was 48.6% with 3.6% complete responses in the previously treated population including 48.2% overall response rate with 3.6%

complete response in the anthracycline resistant patients. The median duration of response was 30 weeks in the previously untreated population, 28 weeks in the previously treated population and 27 weeks in the anthracycline resistant patients. The time to treatment failure was 21 weeks in the previously untreated population, 19 weeks in the previously treated population and 19 weeks in the anthracycline resistant patients.

The 100 mg/m<sup>2</sup> dose is associated with higher toxicity.

There was a high response rate in patients with visceral metastases (53.8% in 78 untreated patients, 55.1% in 69 pre-treated patients and 53.1% in the subgroup of 49 anthracycline resistant patients).

In patients with three or more organs involved, the response rate was 54.3% in previously untreated patients, 55.8% in previously treated patients and 50% in the subgroup of anthracycline resistant patients.

A significant response rate was seen in patients with liver metastases (59.5% in untreated patients, 47.2% in previously treated patients and 40% in the subgroup of anthracycline resistant patients). The same activity is maintained in patients with visceral involvement (70.4% in previously untreated patients, 63.6% in previously treated patients and 63.2% in the subgroup of anthracycline resistant patients).

#### *Patients treated at 100 mg/m<sup>2</sup>. Phase III trials*

Two randomized phase III comparative studies, involving a total of 326 alkylating agent failure and 392 anthracycline failure metastatic breast cancer patients, have been performed with docetaxel 100 mg/m<sup>2</sup> administered every three weeks for seven and ten cycles, respectively.

In alkylating agent failure patients, there were no significant differences in median time to progression or median survival between docetaxel (D; n = 161) and doxorubicin (DX; n = 165; 75 mg/m<sup>2</sup> every three weeks) on intent to treat and evaluable patient analyzes. For the intent to treat analysis, median time to progression was 5.9 months for docetaxel and 4.9 months for doxorubicin (D-DX diff: 1.0 month; 95% confidence interval (CI) for diff: -0.5 to 1.9); median overall survival was 14.7 months for docetaxel and 14.3 months for doxorubicin (D-DX diff: 0.4 months; 95% CI for diff: -1.9 to 2.7). There was a significant difference in response rates between the two groups: 47.8% for docetaxel and 33.3% for doxorubicin (D-DX diff: 14.5%, 95% CI for diff: 3.9 to 25.0) in the intent to treat analysis.

In anthracycline failure patients, docetaxel (n = 203) was compared to the combination of mitomycin C and vinblastine (MV; n = 189; 12 mg/m<sup>2</sup> every six weeks and 6 mg/m<sup>2</sup> every three weeks, respectively). For the intent to treat analysis, docetaxel increased response rate (30% versus 11.6%; D-MV diff: 18.4%; 95% CI for diff: 10.6 to 26.2), prolonged median time to progression (4.3 months versus 2.5 months; D-MV diff: 1.8 months; 95% CI for diff: 1.0 to 2.4) and prolonged median overall survival (11.5 months versus 8.7 months; D-MV diff: 2.8 months; 95% CI for diff: 0.1 to 4.3). Similar results were observed in the evaluable patient analysis.

An open label, multicenter, randomized phase III study was conducted to compare docetaxel and paclitaxel in the treatment of advanced breast cancer in patients whose previous therapy should have included an anthracycline. A total of 449 patients were randomized to receive either docetaxel 100 mg/m<sup>2</sup> as a one-hour infusion or paclitaxel 175 mg/m<sup>2</sup> as a three-hour

infusion. Both regimes were administered every three weeks. Efficacy results are described in Table 12.

**Table 12: Efficacy of docetaxel versus paclitaxel in the treatment of advanced breast cancer (intent-to-treat analysis, unless specified)**

Endpoint	docetaxel 100 mg/m <sup>2</sup> n=225	paclitaxel 175 mg/m <sup>2</sup> n=224	p-value (unadjusted)
Median Survival (months) 95% CI	15.3 (13.3 – 18.5)	12.7 (10.5 – 14.8)	0.03
Median time to progression (weeks) 95% CI	24.6 (20 - 30.1)	15.6 (13.4 – 18.1)	<0.01
*Overall Response Rate (ORR) (%) 95% CI	32.0 (25.9 – 38.1)	25.0 (19.3 – 30.7)	0.10
*ORR in the evaluable population (%) 95% CI	37.0 (30.2 – 43.9)	26.0 (19.9 – 31.9)	0.01

\* Primary study endpoint

The most frequent adverse events reported for docetaxel were neutropenia, febrile neutropenia, gastrointestinal disorders, neurological disorders, asthenia and fluid retention. More grade 3/4 events were observed from docetaxel (55.4%) compared to paclitaxel (23.0%). No unexpected toxicities were reported for docetaxel.

#### *Combination with capecitabine*

Docetaxel in combination with capecitabine was assessed in an open label, multicenter, randomized trial. A total of 511 patients with locally advanced and/or metastatic breast cancer resistant to, or recurring after an anthracycline containing therapy, or relapsing during or recurring within two years of completing an anthracycline containing adjuvant therapy were enrolled. In this trial, 255 patients were randomized to receive capecitabine (1,250 mg/m<sup>2</sup> twice daily for two weeks followed by a one-week rest period) in combination with docetaxel (75 mg/m<sup>2</sup> as a one-hour intravenous infusion every three weeks). 256 patients received docetaxel 100 mg/m<sup>2</sup> alone.

Docetaxel in combination with capecitabine resulted in statistically significant improvements in time to disease progression, overall survival and objective response rate compared to monotherapy with docetaxel as shown in Table 13. Health related quality of life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ), (C30 version 2, including Breast Cancer Module BR23). HRQoL was similar in the two treatment groups.

**Table 13: Breast cancer combination treatment efficacy results<sup>1</sup>**

Endpoint parameter	Capecitabine/ docetaxel N=255	Docetaxel N=256	Difference	p-value
Time to Disease Progression Median [95% CI]	186 days [165, 198]	128 days [105, 136]	HR <sup>2</sup> =0.643 [0.563, 0.770]	0.0001
Survival median [95% CI]	418 days [374, 492]	338 days [298, 362]	HR <sup>2</sup> = 0.753 [0.603, 0.940]	0.0119
Response Rate [95% CI]	41.6% [35.5, 47.9]	29.7% [24.2, 35.7]	11.9% [3.4, 20.0]	0.0058

<sup>1</sup>All randomized population, Investigator assessment

<sup>2</sup> Hazard Ratio

### *Combination with trastuzumab (HER2+)*

Docetaxel in combination with trastuzumab was studied for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously had not received chemotherapy for metastatic disease. One hundred and eighty six patients received docetaxel (100 mg/m<sup>2</sup>) with or without trastuzumab; 60% of patients received prior anthracycline based adjuvant chemotherapy. Docetaxel plus trastuzumab was efficacious in patients whether or not they had received prior adjuvant anthracyclines. The main test used to determine HER2 positivity in this pivotal trial was immunohistochemistry (IHC). A minority of patients were tested using fluorescence *in situ* hybridization (FISH). In this trial, 87% of patients had disease that was IHC 3+, and 95% of patients entered had disease that was IHC 3+ and/or FISH positive. Efficacy results are summarized in Table 14.

**Table 14: Efficacy outcomes in docetaxel + trastuzumab combination therapy**

Parameter	docetaxel plus trastuzumab <sup>1</sup> n=92	docetaxel <sup>1</sup> n=94
Reponses rate (95% CI) p-value**	61% (50, 71)	34% (25, 45)
	p = 0.0002	
Median duration of response (months) (95% CI) p-value*	11.4 (9.2, 15.0)	5.1 (4.4, 6.2)
	p = 0.0002	
Median TTP (months) (95% CI) p-value*	10.6 (7.6, 12.9)	5.7 (5.0, 6.5)
	p = 0.0001	
Median survival (months) (95% CI) p-value*	30.5 (26.8, ne) <sup>2</sup>	22.1 (17.6, 28.9) <sup>2</sup>
	p = 0.0062	

<sup>1</sup> Full analysis (intent-to-treat) <sup>2</sup> Estimated median survival \* p: log-rank test.

\*\* p: Chi-square test. TTP: time to progression. 'ne' indicates that it could not be estimated or was not yet reached.

### Adjuvant Treatment of Breast Cancer

#### *Combination with doxorubicin and cyclophosphamide*

Data from a multicenter open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with node positive breast cancer and KPS (Karnofsky Performance Score) greater than or equal to 80%, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1,491 patients were randomized to receive either docetaxel 75 mg/m<sup>2</sup> administered one hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (TAC arm), or doxorubicin 50 mg/m<sup>2</sup> followed by fluorouracil 500 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (FAC arm). Both regimens were administered once every three weeks for six cycles. Docetaxel was administered as a one-hour infusion; all other drugs were given as IV (intravenous) bolus on day 1. G-CSF was administered in both arms as secondary prophylaxis to patients who experienced febrile neutropenia, prolonged neutropenia or neutropenic infection. Patients in the docetaxel arm who continued to experience these reactions remained on G-CSF and had their dose reduced to 60 mg/m<sup>2</sup>. Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally b.i.d. (twice daily) for ten days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to five years. Adjuvant radiation therapy was

prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

An interim analysis was performed with a median follow-up of 55 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. In the TAC arm, 23% of subjects had experienced disease progression, compared to 30% in the FAC arm. TAC treated patients had a 28% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.72, 95% CI (0.59 to 0.88),  $p = 0.001$ ). Overall survival was also significantly longer in the TAC arm, with TAC treated patients having a 30% reduction in the risk of death compared to FAC (hazard ratio = 0.70, 95% CI (0.53 to 0.91),  $p = 0.008$ ). In the TAC arm, 12% of patients had died compared to 17% on the FAC arm.

In the adjuvant breast cancer trial (TAX 316), 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.

TAC treated patient subsets according to prospectively defined major prognostic factors were analyzed (see Table 15).

**Table 15: Analysis of TAC treated patient subsets**

Patient subset	Number of patients	Disease free survival			Overall survival		
		Hazard ratio*	95% CI	P	Hazard ratio*	95% CI	P
<b>No of positive nodes</b>							
Overall	745	0.72	0.59–0.88	0.001	0.70	0.53-0.91	0.008
1-3	467	0.61	0.46-0.82	0.0009	0.45	0.29-0.70	0.0002
4+	278	0.83	0.63-1.08	0.17	0.94	0.66-1.33	0.72
<b>Hormone receptor status</b>							
Positive	567	0.72	0.56-0.92	0.0076	0.69	0.48-1.00	0.0459
Negative	178	0.69	0.49-0.97	0.0296	0.66	0.44-0.98	0.0389
<b>Her-2 neu status</b>							
Positive	155	0.60	0.41-0.88	0.0088	0.74	0.45-1.20	0.22
Negative	475	0.76	0.59-1.00	0.046	0.63	0.44-0.91	0.0135

\* A hazard ratio of less than 1 indicates that TAC is associated with a longer disease free survival and overall survival compared to FAC

The beneficial effect of TAC was seen in both hormone receptor positive and negative patients.

*Combination with doxorubicin, cyclophosphamide and trastuzumab and with carboplatin and trastuzumab (HER2+)*

The efficacy and safety of docetaxel in combination with trastuzumab was studied for the adjuvant treatment of patients with operable breast cancer whose tumors overexpress HER2 (with node positive and high risk node negative). A total of 3,222 women were randomized in the study, and 3,174 were treated with either: AC-T, AC-TH or TCH.

**AC-T (control arm).** Doxorubicin 60 mg/m<sup>2</sup> IV in combination with cyclophosphamide 600 mg/m<sup>2</sup> IV every 3 weeks for 4 cycles, followed by docetaxel 100 mg/m<sup>2</sup> as a 1-hour IV infusion every 3 weeks for 4 cycles.

**AC-TH.** Doxorubicin 60 mg/m<sup>2</sup> IV in combination with cyclophosphamide 600 mg/m<sup>2</sup> IV every 3 weeks for 4 cycles. Three weeks after the last cycle of AC, trastuzumab 4 mg/kg loading dose by IV infusion over 90 minutes on day 1 of cycle 5 was administered, followed by trastuzumab 2 mg/kg by IV infusion over 30 minutes weekly starting day 8 of cycle 5; and docetaxel 100 mg/m<sup>2</sup> administered by IV infusion over 1 hour on day 2 of cycle 5, then on day 1 every 3 weeks for a total of 4 cycles of docetaxel. Beginning three weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg by IV infusion over 30 minutes was given every 3 weeks (for 1 year from the date of first administration).

**TCH.** Trastuzumab 4 mg/kg loading dose by IV infusion over 90 minutes on day 1 of cycle 1 only, followed by trastuzumab 2 mg/kg by IV infusion over 30 minutes weekly starting on day 8 until three weeks after the last cycle of chemotherapy. Docetaxel 75 mg/m<sup>2</sup> was administered on day 2 of cycle 1, then on day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin (AUC 6 mg/mL/min) as a 30-60-minute IV infusion, for a total of six cycles of docetaxel and carboplatin. Beginning three weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg by IV infusion over 30 minutes was given every 3 weeks (for 1 year from the date of first administration).

The patients and disease characteristics at baseline were well balanced between the 3 treatment arms.

Disease free survival (DFS) was the primary endpoint, and overall survival (OS) was the secondary endpoint.

Results of the second interim analysis, performed with a median follow-up of 36 months, demonstrated that docetaxel and trastuzumab given concurrently as part of either an anthracycline based (AC-TH) or non-anthracycline based (TCH) adjuvant treatment regimens, for patients with HER2 positive operable breast cancer, statistically prolonged both DFS and OS compared with the control arm (AC-T). The AC-TH and TCH regimens significantly improved disease free survival compared with AC-T at the significance level of 0.003 required for the interim analysis. Overall survival was significantly better with AC-TH but not TCH compared to AC-T in the interim analysis. There was no statistically significant difference between the two trastuzumab containing arms AC-TH and TCH for DFS and OS. Efficacy results are summarized in Table 16.

**Table 16: Doxorubicin and cyclophosphamide followed by docetaxel in combination with trastuzumab, or docetaxel in combination with trastuzumab and carboplatin (intent to treat population).**

	Disease Free Survival (DFS)			Overall Survival (OS)		
	AC-T n=1073	AC-TH n=1074	TCH n=1075	AC-T n=1073	AC-TH n=1074	TCH n=1075
Stratified analysis						
Hazard ratio <sup>a</sup>	NA	0.61	0.67	NA	0.58	0.66
95% CI	NA	(0.49-0.77)	(0.54-0.83)	NA	(0.40-0.83)	(0.47-0.93)

	Disease Free Survival (DFS)			Overall Survival (OS)		
	AC-T n=1073	AC-TH n=1074	TCH n=1075	AC-T n=1073	AC-TH n=1074	TCH n=1075
p-value <sup>b</sup>	NA	<0.0001	0.0003	NA	0.0024	0.0182
Percent event free at 3 years (95% CI)	80.9% (78.3-83.5%)	86.7% (84.4-89.0%)	85.5% (83.2-87.9%)	93.0% (91.2-94.8%)	95.5% (94.0-96.9%)	95.2% (93.7-96.6%)
Absolute benefit <sup>c</sup>		5.8% (2.3-9.2%)	4.6% (1.2-8.1%)		2.5% (0.2-4.8%)	2.2% (-0.1-4.5%)

AC-T = doxorubicin plus cyclophosphamide, followed by docetaxel; AC-TH = doxorubicin plus cyclophosphamide, followed by docetaxel in combination with trastuzumab; TCH = docetaxel in combination with trastuzumab and carboplatin; CI = confidence interval; NA=not applicable

<sup>a</sup> = Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status;

<sup>b</sup> = Stratified log-rank p-value;

<sup>c</sup> = Absolute benefit in percent event free compared to AC-T at 3 years.

There were 29% of patients with high risk node negative disease included in the study. The benefit observed for the overall population was irrespective of the nodal status. See Table 17.

**Table 17: Disease free survival (intent to treat population) according to nodal status**

	High risk node negative patients			Node positive patients		
	AC-T n=309	AC-TH n=306	TCH n=307	AC-T n=764	AC-TH n=768	TCH n=768
Stratified analysis						
Hazard ratio <sup>a</sup>	NA	0.36	0.52	NA	0.67	0.70
95% CI	NA	(0.19-0.68)	(0.30-0.92)	NA	(0.53-0.85)	(0.56-0.89)
p-value <sup>b</sup>	NA	0.0010	0.0209	NA	0.0008	0.0029
Percent event free at 3 years (95% CI)	88.0% (84.1-91.9%)	94.8% (91.9-97.8%)	93.0% (89.9-96.2%)	78.1% (74.9-81.3%)	83.6% (80.7-86.5%)	82.6% (79.6-85.6%)
Absolute benefit <sup>c</sup>		6.8% (1.9-11.7%)	5.1% (0.0-10.1%)		5.5% (1.2-9.8%)	4.6% (0.2-8.9%)

AC-T = doxorubicin plus cyclophosphamide, followed by docetaxel

AC-TH = doxorubicin plus cyclophosphamide, followed by docetaxel in combination with trastuzumab

TCH = docetaxel in combination with trastuzumab and carboplatin

CI = confidence interval

NA = not applicable

<sup>a</sup> = Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status;

<sup>b</sup> = Stratified log-rank p-value

<sup>c</sup> = Absolute benefit in percent event free compared with AC-T

### *Combination with Cyclophosphamide*

Docetaxel in combination with cyclophosphamide (TC) was investigated in a phase III randomized prospective clinical trial, in comparison with the standard treatment regimen of doxorubicin and cyclophosphamide (AC). Results of the trial were only available in the form of two published papers. A total of 1016 patients with operable stage I to III invasive breast

cancer were randomly assigned to receive either four cycles of AC (60 and 600 mg/m<sup>2</sup> respectively every three weeks; n=510), or four cycles of TC (75 mg and 600 mg/m<sup>2</sup> every three weeks; n=506) as adjuvant chemotherapy after complete surgical excision of the primary tumor. Patients had to have a primary tumor of  $\geq 1$  cm and  $< 7$  cm, and no evidence of metastatic disease. Neoadjuvant chemotherapy was not permitted.

Both treatment groups were well balanced for major prognostic factors; including age, race, stage, histology, hormone receptor status and nodal status. On completion of four cycles of chemotherapy (with or without radiotherapy) tamoxifen was administered to all patients with hormone receptor positive breast cancer for 5 years.

After median follow up of 5 years, the results demonstrated an improvement in disease free survival (DFS) for TC compared with AC. In the TC arm 435/506 (86%) remained alive and disease-free, compared to 408/510 (80%) in the AC arm (HR = 0.67; 95% CI 0.50 to 0.94; p=0.015).

### ***Non-Small Cell Lung Cancer***

#### Patients treated at 75 mg/m<sup>2</sup>

One phase II study was conducted in 20 previously untreated patients with locally advanced or metastatic non-small cell lung cancer. In this clinical trial, docetaxel was administered at a dose of 75 mg/m<sup>2</sup> given as a one-hour infusion every three weeks. The response rate was 10%.

#### Patients treated at 100 mg/m<sup>2</sup>

Six phase II studies were conducted in patients with locally advanced or metastatic non-small cell lung cancer. A total of 160 patients had received no prior chemotherapy (previously untreated) and 88 patients had received prior platinum based chemotherapy (previously treated) which included 37 patients who had progressive disease with platinum therapy (platinum refractory). In these clinical trials, docetaxel was administered at a dose of 100 mg/m<sup>2</sup> given as a one-hour infusion every three weeks.

The 100 mg/m<sup>2</sup> dose is associated with higher toxicity.

In the intent to treat analysis on previously untreated patients, the overall response rate was 26.9% and in the previously treated population it was 17%. The survival time for all previously untreated patients or previously treated patients was nine and eight months, respectively.

### ***Ovarian Cancer***

#### Patients treated at 100 mg/m<sup>2</sup>

Docetaxel was studied in five uncontrolled trials in patients with advanced epithelial ovarian cancer who had failed previous treatment with cisplatin or carboplatin. These patients (n = 377) received docetaxel 100 mg/m<sup>2</sup> in a one-hour intravenous infusion every three weeks.

In the intent to treat analysis, median time to progression ranged from 9.2 to 13.1 weeks, median survival ranged from 7 to 10.3 months, overall response rate ranged from 8.3 to 24.0% and complete response rate ranged from 2.8 to 8.3%.

### ***Prostate Cancer***

The safety and efficacy of docetaxel in patients with androgen independent (hormone refractory) metastatic prostate cancer were evaluated in a randomized multicenter phase III trial. A total of 1,006 patients with KPS greater than or equal to 60 were randomized to the following treatment groups:

- Docetaxel 75 mg/m<sup>2</sup> every three weeks for ten cycles;
- Docetaxel 30 mg/m<sup>2</sup> administered weekly for the first five weeks in a six-week cycle for five cycles;
- Mitozantrone 12 mg/m<sup>2</sup> every three weeks for ten cycles.

All three regimens were administered in combination with prednisone or prednisolone 5 mg twice daily, continuously.

Patients who received docetaxel every three weeks demonstrated significantly longer overall survival compared to those treated with mitozantrone (p = 0.0094). The increase in survival seen in the docetaxel weekly arm was not statistically significant compared to the mitozantrone control arm. Efficacy endpoints for the docetaxel three weekly arm versus the control arm are summarized in Table 18.

**Table 18: Efficacy of docetaxel in the treatment of patients with androgen independent (hormone refractory) prostate cancer (intent to treat analysis)**

Endpoint	Docetaxel Every 3 weeks	Mitozantrone Every 3 weeks
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	-
95% CI	(0.619-0.936)	-
p-value <sup>+</sup>	0.0094	-
Number of patients	291	300
PSA** response rate (%)	45.4	31.7
95% CI	(39.5-51.3)	(26.4-37.3)
p-value*	0.0005	-
Number of patients	153	157
Pain response rate (%)	34.6	21.7
95% CI	(27.1-42.7)	(15.5-28.9)
p-value*	0.0107	-
Number of patients	141	137
Tumor response rate (%)	12.1	6.6
95% CI	(7.2-18.6)	(3.0-12.1)
p-value*	0.1112	-

<sup>+</sup> Stratified log rank test. \* Threshold for statistical significance = 0.0175. \*\* PSA: Prostate Specific Antigen.

## ***Head and Neck Cancer***

### **Induction therapy followed by radiotherapy (TAX 323)**

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) were evaluated in a phase III, multicenter, open label, randomized trial (TAX 323). In this study, 358 previously untreated patients with locally advanced inoperable stage III/IV SCCHN and World Health Organization (WHO) performance

status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m<sup>2</sup> followed by cisplatin (P) 75 mg/m<sup>2</sup> on day 1, followed by fluorouracil (F) 750 mg/m<sup>2</sup> per day as a continuous infusion on days 1 to 5. The cycles were repeated every three weeks for four cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin 100 mg/m<sup>2</sup> on day 1, followed by fluorouracil 1,000 mg/m<sup>2</sup> (PF) as a continuous infusion on days 1 to 5. The cycles were repeated every three weeks for four cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of four weeks and a maximal interval of seven weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines.

Conventional locoregional radiotherapy was given to approximately 77% of the patients at a total dose of 66 to 70 Gy (1.8 to 2.0 Gy once a day, five days/week) while accelerated/hyperfractionated regimens of radiation therapy were used in approximately 23% of patients (twice a day, with a minimum interfraction interval of six hours, five days/week).

A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy. The primary endpoint in this study, progression free survival (PFS), was significantly longer in the TPF arm compared to the PF arm,  $p = 0.0042$  (median PFS: 11.4 versus 8.3 months, respectively) with an overall median follow-up time of 33.7 months. Median overall survival (OS) was significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 versus 14.5 months, respectively) with a 28% risk reduction of mortality,  $p = 0.0128$ . Patients with tumors of the nasopharynx and the nasal/ paranasal cavities were excluded from this study. Efficacy results are presented in Table 19.

**Table 19: Efficacy of docetaxel in the induction treatment of patients with locally advanced inoperable SCCHN (intent-to-treat analysis)**

Endpoint	Docetaxel + cis + FU n=177	Cis + FU n=181
Median progression free survival (months) (95% CI)	11.4 (10.1 - 14.0)	8.3 (7.4 - 9.1)
Adjusted Hazard Ratio (95% CI) * p-value	0.70 (0.55 - 0.89) 0.0042	
Median survival (months) (95% CI)	18.6 (15.7 - 24.0)	14.5 (11.6 - 18.7)
Hazard Ratio (95% CI) ** p-value	0.72 (0.56 - 0.93) 0.0128	
Overall response rate to chemotherapy (%) (95% CI) *** p-value	67.8 (60.4 - 74.6)	53.6 (46.0 - 61.0)
	0.006	
Overall response rate to study treatment (chemo ± radiotherapy) (%) (95% CI) *** p-value	72.3 (65.1 - 78.8)	58.6 (51.0 - 65.8)
	0.006	

Endpoint	Docetaxel + cis + FU n=177	Cis + FU n=181
Median duration of response to chemo ± radiotherapy (months) (95% CI)	n=128 15.7 (13.4 – 24.6)	n=106 11.7 (10.2-17.4)
Hazard Ratio (95% CI)	0.72 (0.52 - 0.99)	
** p-value	0.0457	

A Hazard Ratio of less than 1 favors docetaxel + cisplatin + FU. \*Cox model (adjustment for primary tumor site, T and N clinical stages and PSWHO). \*\*Log-rank test. \*\*\* Chi-square test

### *Clinical benefit parameters*

Patients treated with TPF experienced significantly less deterioration of their global health score compared to those treated with PF (p = 0.01, using EORTC QLQ-C30).

The performance status scale for head and neck, designed to measure disturbances of speech and eating, was significantly in favor of TPF treatment.

The median time to first deterioration of WHO performance status was significantly (p = 0.0158) longer in the TPF arm (13.7 months; 95% CI: 10.7 to 21.0 months) compared to PF (8.3 months; 95% CI: 7.3 to 9.6 months). However, no significant difference in WHO performance status was apparent between the two arms (odds ratio = 0.96, 95% CI: 0.66 to 1.41). There was no difference in pain intensity in patients treated with TPF or PF.

### Induction chemotherapy followed by chemoradiotherapy (TAX 324)

The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, or candidates for organ preservation) SCCHN was evaluated in a randomized, multicenter open label, phase III trial (TAX 324). Patients with tumors of the nasopharynx and nasal/ paranasal cavities were excluded from this study. In this study, 501 patients with locally advanced SCCHN, and a WHO performance status of 0 or 1 were randomized to one of two arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m<sup>2</sup> by IV infusion on day 1, followed by cisplatin (P) 100 mg/m<sup>2</sup> administered as a 30-minute to three-hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1,000 mg/m<sup>2</sup>/day from day 1 to day 4. The cycles were repeated every three weeks for three cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100 mg/m<sup>2</sup> administered as a 30-minute to three-hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1,000 mg/m<sup>2</sup>/day from day 1 to day 5. The cycles were repeated every three weeks for three cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).

Patients in both treatment arms were to receive seven weeks of CRT following induction chemotherapy with a minimum interval of three weeks and no later than eight weeks after start of the last cycle (day 22 to day 56 of last cycle). During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour IV infusion for a maximum of seven doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, five days per week for seven weeks, for a total dose of 70 to 72 Gy). Surgery on the primary site of disease and/or neck could be considered at any time following completion of CRT.

The primary efficacy endpoint in this study, OS was significantly longer (log rank test p = 0.0058) with the docetaxel containing regimen compared to PF (median OS: 70.6 versus 30.1

months, respectively), with a 30% risk reduction in mortality compared to PF (hazard ratio (HR)= 0.70, 95% CI = 0.54 to 0.90). The secondary endpoint PFS demonstrated a 29% risk reduction of progression or death and a 22-month improvement in median PFS (35.5 months for TPF and 13.1 for PF). This was also statistically significant with an HR of 0.71; 95% CI 0.56 to 0.90; log rank test p = 0.004. Efficacy results are presented in Table 20.

**Table 20: Efficacy of docetaxel in the induction treatment followed by chemoradiotherapy for patients with locally advanced SCCN (intent to treat analysis)**

Endpoint	Docetaxel + Cis + FU n=255	Cis + FU n=246
Median overall survival (months) (95% CI)	70.6 (49.0 – N/A)	30.1 (20.9 – 51.5)
Hazard Ratio (95% CI) *p-value	0.70 (0.54 – 0.90) 0.0058	
Median progression free survival (months) (95% CI)	35.5 (19.3 – N/A)	13.1 (10.6 – 20.2)
Hazard Ratio (95% CI) ** p-value	0.71 (0.56 – 0.90) 0.004	
Best overall response (CR + PR) to induction chemotherapy (%) (95% CI) *** p-value	71.8 (65.8 – 77.2)	64.2 (57.9 – 70.2)
	0.070	
Best overall response (CR + PR) to study treatment [induction chemotherapy ± chemoradiotherapy] (%) (95% CI) *** p-value	76.5 (70.8 – 81.5)	71.5 (65.5 – 77.1)
	0.209	

A Hazard Ratio of less than 1 favors docetaxel + cisplatin + FU. \* Unadjusted log-rank test.

\*\* Unadjusted log-rank test, not adjusted for multiple comparisons. \*\*\* Chi-square test, not adjusted for multiple comparisons. N/A – not applicable.

## 5.2 Pharmacokinetic properties

### Absorption

Docetaxel 10 mg/mL Solution for Infusion (IV) is administered by intravenous infusion. By definition, absorption is complete at the end of the infusion.

### Distribution

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5 to 115 mg/m<sup>2</sup> in phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11.1 hours, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100 mg/m<sup>2</sup> dose given as a one-hour infusion, a mean peak plasma level of 3.7 microgram/mL was obtained with a corresponding area under the curve (AUC) of 4.6 hour.microgram/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/hour/m<sup>2</sup> and 113 L, respectively.

### Metabolism and excretion

A study of  $^{14}\text{C}$ -docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group; within seven days, the urinary and fecal excretion account for about 6 and 75% of the administered radioactivity, respectively. About 80% of the radioactivity (60% of the administered dose) recovered in feces is excreted during the first 48 hours as one major and three minor inactive metabolites and very low amounts of unchanged drug.

A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not altered by the age or sex of the patient. In a small number of patients ( $n = 23$ ) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST greater than or equal to 1.5 times the upper limit of normal, associated with alkaline phosphatase greater than or equal to 2.5 times the upper limit of normal), total clearance was lowered by, on average, 27% (see **Section 4.2 Dosage and method of administration**). Docetaxel clearance was not modified in patients with mild to moderate fluid retention. No data are available in patients with severe fluid retention.

Docetaxel is more than 95% bound to plasma proteins. Dexamethasone did not affect protein binding of docetaxel.

The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of docetaxel was observed.

Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and the effect of docetaxel on the pharmacokinetics of capecitabine showed no effect of capecitabine on the pharmacokinetics of docetaxel ( $C_{\text{max}}$  and AUC) and no effect of docetaxel on the pharmacokinetics of the main capecitabine metabolite 5'DFUR.

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

### 5.3 Preclinical safety data

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumor cell lines and against freshly excised human tumor cells in clonogenic assays. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some, but not all, cell lines overexpressing the p-glycoprotein, which is encoded by the multidrug resistance gene. *In vivo*, docetaxel is schedule independent and has a broad spectrum of experimental antitumor activity against advanced murine and human grafted tumors. Against transplantable murine tumors *in vivo*, docetaxel was synergistic with vincristine (administered at the same time), etoposide, cyclophosphamide or fluorouracil, but not with vincristine (administered 24 hours apart), cisplatin or doxorubicin.

#### Genotoxicity

Docetaxel was not mutagenic in bacterial or CHO/HPRT gene mutation assays, but induced chromosomal aberrations in the *in vitro* chromosome aberration assay and in the *in vivo* micronucleus test in the mouse.

**Carcinogenicity**

The carcinogenic potential of docetaxel has not been studied. However, based upon its pharmacodynamic mechanism of action, docetaxel may be a carcinogen.

**6.0 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Ethanol  
Citric acid  
Polysorbate 80  
Macrogol 300

**6.2 Shelf life**

Please see outer package for expiry date of the product.

**6.3 Storage condition(s)**

Store at temperatures not exceeding 25°C.

**6.4 Availability**

Type I Clear and Colorless Glass vial x 2 mL and 8 mL (Box of 1's).

**6.5 Special precautions for disposal and other handling**

Any unused medicine or waste material should be disposed in accordance with local requirements.

**6.6 Incompatibilities**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

**7.0 FDA REGISTRATION NUMBER**

10 mg/mL Solution for Infusion (IV): DR-XY39743

**8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

10 mg/mL Solution for Infusion (IV): 05 November 2015

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: [www.fda.gov.ph](http://www.fda.gov.ph)

Seek medical attention immediately at the first sign of any adverse drug reaction.

**CAUTION:** Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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