NEW ZEALAND DATA SHEET
DOCETAXEL ACCORD (DOCETAXEL) CONCENTRATED INJECTION

1 PRODUCT NAME

Docetaxel Accord 20 mg/1 mL concentrated solution for injection

Docetaxel Accord 80 mg/4 mL concentrated solution for injection

Docetaxel Accord 160 mg/8 mL concentrated solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of docetaxel solution contains 20 mg docetaxel.

Single-dose vials of Docetaxel Concentrated Injection contain 20 mg/1 mL, 80 mg/4 mL or 160 mg/8 mL of docetaxel.

Excipients with known effect

Absolute ethanol 395 mg/mL.

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

3 PHARMACEUTICAL FORM

Docetaxel Accord is a sterile pyrogen-free non-aqueous pale yellow to brownish-yellow concentrated solution for injection. It must be diluted prior to intravenous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Breast cancer

Docetaxel Accord is indicated for the treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed.

Docetaxel Accord 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 Accord in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

Adjuvant treatment of breast cancer

Docetaxel Accord 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 Accord in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

Docetaxel Accord in combination with carboplatin and trastuzumab (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

Docetaxel Accord in combination with cyclophosphamide is indicated for the adjuvant treatment of operable breast cancer with a primary tumour of ≥ 1 cm and < 7 cm.

Non small cell lung cancer

Docetaxel Accord is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum-based chemotherapy.

Ovarian cancer

Docetaxel Accord is indicated for the treatment of metastatic carcinoma of the ovary after failure of first-

line or subsequent chemotherapy.

Prostate cancer

Docetaxel Accord is indicated for the treatment of patients with androgen independent (hormone refractory) prostate cancer.

Head and neck cancer

Docetaxel Accord, in combination with cisplatin and fluorouracil, 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 tumour is technically unresectable.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended dosage

Breast cancer

Metastatic breast cancer

Monotherapy

The recommended dosage of docetaxel is 75 to 100 mg/m^2 administered as a one-hour infusion every three weeks (see **Section 6.6 Special Precautions for Disposal and Other Handling**). A dose of 100 mg/m^2 has been shown to result in a moderate increase in response rates compared with 75 mg/m^2 but is associated with greater toxicity.

Combination with capecitabine

The recommended dosage of docetaxel is 75 mg/m^2 administered as a one-hour infusion every three weeks when combined with capecitabine administered orally at 1,250 mg/m^2 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 dose is 100 mg/m^2 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 in the adjuvant treatment of breast cancer is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for a total of six cycles (see **section Dosage adjustments during treatment** and **Section 4.4 Special Warnings and Precautions for Use, Haematology**).

Combination with Trastuzumab following Doxorubicin and Cyclophosphamide (HER2+)

AC-TH

AC (cycles 1 – 4): doxorubicin (A) 60 mg/m^2 followed by cyclophosphamide (C) 600 mg/m^2 administered every three weeks for 4 cycles.

TH (cycles 5 – 8): docetaxel (T) 100 mg/m^2 administered every three weeks for 4 cycles, and trastuzumab (H) administered weekly according 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^2; days 8 and 15: trastuzumab 2 mg/kg.

Cycles 6 – 8: Day 1: docetaxel 100 mg/m^2 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^2 and carboplatin (C) at AUC of 6 mg/mL/min administered every three weeks and trastuzumab (H) administered weekly according the following schedule:

Cycle 1: Day 1: trastuzumab 4 mg/kg (loading dose); day 2: docetaxel 75 mg/m^2 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^2 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 is docetaxel 75 mg/m^2 over 1 hour and cyclophosphamide 600 mg/m^2 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 and continuing for a total of five doses.

Non small cell lung cancer

The recommended dosage of docetaxel is 75 to 100 mg/m^2 administered as a one-hour infusion every three weeks (see **Section 6.6 Special Precautions for Disposal and Other Handling**). A dose of 100 mg/m^2 has been shown to result in a moderate increase in response rates compared with 75 mg/m^2 but is associated with greater toxicity.

Ovarian cancer

The recommended dosage of docetaxel is 75 to 100 mg/m^2 administered as a one-hour infusion every three weeks (see **Section 6.6 Special Precautions for Disposal and Other Handling**). A dose of 100 mg/m^2 has been shown to result in a moderate increase in response rates compared with 75 mg/m^2 but is associated with greater toxicity.

Prostate cancer

Metastatic castration-resistant prostate cancer

The recommended dosage of docetaxel for prostate cancer is 75 mg/m^2 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 is 75 mg/m^2 as a one hour infusion followed by cisplatin 75 mg/m^2 over one hour, on day one, followed by fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

Induction chemotherapy followed by chemoradiotherapy (TAX 324)

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion

on day 1, followed by cisplatin 100 mg/m^2 administered as a 30 minute to 3 hour infusion, followed by fluorouracil 1000 mg/m^2 as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy.

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

A premedication consisting of an oral corticosteroids, such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 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, 3 hours and 1 hour before the docetaxel infusion.

Dosage adjustments during treatment

Docetaxel should be administered when the neutrophil count is ≥ 1.5 cells x 10^9/L.

In patients treated at 75 mg/m^2

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells x 10^9/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^2 to 55 mg/m^2 (or to 60 mg/m^2 for adjuvant therapy for breast cancer). If the patient continues to experience these reactions at 55 mg/m^2 (or at 60 mg/m^2), the treatment should be discontinued.

In patients treated at 100 mg/m^2

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells x 10^9/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^2 to 75 mg/m^2. If the patient continues to experience these reactions at 75 mg/m^2, the dosage should either be decreased from 75 mg/m^2 to 55 mg/m^2, 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 0-1, 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 0-1, then resume treatment with docetaxel 55mg/m^2.

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 dose is 100mg/m^2 every three weeks, with trastuzumab administered weekly. For trastuzumab dosage and administration, see the 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 leukaemia requires haematological 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 60mg/m^2. If G-CSF is not used, the docetaxel dose should be reduced from 75 to 60mg/m^2. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m^2.

Patients treated with docetaxel in AC-TH or TCH

Patients who received AC-TH or TCH adjuvant therapy for operable breast cancer whose tumours 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^2 to 75 mg/m^2 (in the AC-TH regimen); docetaxel will be reduced from 75 mg/m^2 to 60 mg/m^2 (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/m2 to 75 mg/m2 (in the AC-TH regimen) or from 75 mg/m2 to 60 mg/m² (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^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2.

In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100, 000 cells/mm^3. Discontinue treatment if these toxicities persist.

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

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

Table 1: Recommended Dose Modifications for Toxicities in Patients Treated with docetaxel in Combination with cisplatin and fluorouracil

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

Use in renal impairment

No information available.

Use in hepatic impairment

Patients with hepatic impairment treated at 75 mg/m^2

For those patients with increased serum bilirubin and/or values > 3.5 times the ULN for ALT and AST and > 6 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^2

Based on the pharmacokinetic data, in patients who have both elevations of transaminase values [ALT and/or AST greater than 1.5 times the upper limit of normal range (ULN)] and increases in alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m2 (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 > 6 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 and the maximum dose for an entire course of therapy

The maximum daily dose is 100mg/m2. The maximum dose per course is not specified.

Children

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

Elderly

Based on the population pharmacokinetics, there are no special instructions for the use in elderly. For capecitabine dosage reduction when combined with docetaxel, see capecitabine Product Information.

Monitoring advice

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

For instructions on dilution of the product before administration and storage of the diluted product see **Section 6.6 Special Precautions for Disposal and Other Handling.**

4.3 CONTRAINDICATIONS

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or any of the excipients.

Docetaxel should not be used in patients with baseline neutrophil count of < 1.5 cells x 10^9/L.

Docetaxel should not be used in patients with severe liver impairment.

Docetaxel should not be used in pregnant or breast-feeding women.

Contraindications that apply for other drugs also apply when these drugs are combined with docetaxel.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of docetaxel should be confined to units specialised 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 administration. A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days starting one day prior to docetaxel administration can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. (see **Fluid retention** and **Hypersensitivity reaction** sections below and refer to **Section 4.2 Dose and Method of Administration**).

For prostate cancer, the premedication is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion.

Haematology

Bone marrow suppression and other haematologic effects to docetaxel include neutropenia, the most frequent adverse reactions 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 pretreated 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 ≥ 1.5 cells x 10^9/L.

Docetaxel should not be administered to patients with baseline neutrophil counts of < 1.5 cells x 10^9/L. Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel. Patients should not be retreated with docetaxel until neutrophils recover to a level ≥ 1.5 cells x 10^9/L. (See **Section 4.2 Dose and Method of Administration**.)

In the case of severe neutropenia (< 0.5 cells x 10^9/L for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended. Prophylactic G-CSF may be used to mitigate the risk of haematological 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 dose reduced (see also **Section 4.2 Dose and Method of Administration, Dosage adjustments during treatment**). Patients receiving TPF and TAC should be closely monitored (see **Section 4.2 Dose and Method of Administration and 4.8 Adverse Effects (Undesirable Effects)**)

In the treatment of adjuvant breast cancer, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological 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 **Sections 4.2 Dose and Method of Administration, 4.4 Special Warnings and Precautions for Use – Haematology** and **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, during or immediately following the cessation of the infusion of docetaxel, 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, dyspnoea and drug fever or chills. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel 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.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a potentially fatal 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 characterised by a rash including localised 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 such as eruptions followed by desquamation which rarely led to interruption or discontinuation of docetaxel treatment were reported. Nail disorders were characterised by hypo- or hyperpigmentation, pain and onycholysis.

Very rare cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, scleroderma-like changes and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis (AGEP) have been reported with docetaxel. 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.

Fluid retention

A premedication consisting of an oral corticosteroid such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 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 Dose and Method of Administration**).

The peripheral oedema usually starts at the lower extremities and may become generalized with a weight gain of 3 kgs 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^2 is 524 mg/m^2 and treatment at 100 mg/m^2 is 509 mg/m^2 (without premedication) and 797 mg/m^2 (with premedication). *Fluid retention is slowly reversible after docetaxel treatment is stopped. In patients treated by docetaxel as single agent, at 100 mg/m^2, the median cumulative dose to treatment discontinuation was more than 1,000 mg/m^2 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 oedema 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 requires a reduction of dose (see **Section 4.2 Dose and Method of Administration**).

The amount of ethanol in Docetaxel Accord should be taken into account when given to patients with epilepsy (see **Section 6.1 List of Excipients**).

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

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.

Ventricular arrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with docetaxel in combination regimens including doxorubicin, fluorouracil and/or cyclophosphamide (see **Section 4.8 Undesirable Effects**).

Prescribers should inform patients to report any irregular and/or rapid heartbeat, severe shortness of breath, dizziness, and/or fainting.

Tumour lysis syndrome

Tumour lysis syndrome has been reported with docetaxel after the first or the second cycle (see **Section 4.8 Undesirable Effects**). Patients at risk of tumour lysis syndrome (e.g. with renal impairment, hyperuricemia, bulky tumour, 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 Medicines and Other Forms of Interactions**).

Eye disorders

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

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 Dose and Method of Administration**).

Gastrointestinal reactions: Early abdominal pain and tenderness, fever, diarrhoea, 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**).

Leukaemia: In the adjuvant treatment of breast cancer, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow up.

Alcohol Content

Docetaxel 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^2 who have both elevations of serum transaminase values (ALT and/or AST) > 1.5 times the upper limit of normal (ULN) and increases in alkaline phosphatase> 2.5 times the ULN, there is a greater risk of developing severe adverse reactions such as toxic deaths including sepsis, gastrointestinal haemorrhage 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^2 (see **Section 4.2 Dose and Method of Administration**).

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. The amount of ethanol in Docetaxel Accord should be taken into account when given to patients with hepatic impairment (see **Section 6.1 List of Excipients**).

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 reactions, treatment-related serious adverse reactions and early withdrawals from treatment due to adverse reactions 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 anaemia, 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. ≥ 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 TAX323 and TAX324 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.

Paediatric use

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

Effects on laboratory tests

See **Section 4.8 Undesirable Effects**.

4.5 INTERACTIONS WITH OTHER MEDICINES 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, α1-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 ethanol in Docetaxel Accord may alter the effects of other medicinal products.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Studies in mice have shown that IV doses of 144 mg/m^2 or 30 mg/m^2/day for 5 days are associated with testicular atrophy, mineralisation and degeneration of tubular germinal epithelium, Leydig cell hyperplasia, epididymal hypospermia, and follicular atresia in the ovaries. Studies in rats have shown that intravenous doses of 120 mg/m^2 are associated with testicular atrophy, germ cell atrophy, Leydig cell hyperplasia and mineralisation. The rodent studies suggest that docetaxel may impair fertility. Studies in rats have also shown that IV doses of 0.9 mg/m^2/day to both sexes are associated with reduced litter averages for corpora lutea, implantations and live foetuses, and increased litter averages for early and total resorptions. Larger doses to both sexes (males 1.8 mg/m^2/day, females 1.35 mg/m^2/day) are additionally associated with increased time to mating, increased number of dams with total resorption, and reduced male foetal body weight.

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: drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations of irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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

Foetal radioactivity has been detected following intravenous (IV) administration of radiolabelled docetaxel to pregnant rats. Docetaxel has been shown to be embryo- and foetotoxic in rats and rabbits. At IV doses of 0.9 mg/m^2, docetaxel caused fewer corpora lutea, fewer implantations, increased resorptions and embryofoetal deaths in rats. No evidence of teratogenic effects was found when docetaxel was administered IV at doses up to 1.8 mg/m^2 or 1.2 mg/m^2 in rats or rabbits, respectively, but reduced foetal weight and delayed ossification were observed.

Offspring from rats receiving docetaxel 1.5 mg/m^2/day IV 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 appraised 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^2/day IV 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 breast-feed during treatment with docetaxel and for one 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 Accord may impair the ability to drive or use machines. The alcohol content in a maximum recommended dose of 200 mg (based on 100 mg/m^2, body surface area of 2.0 m^2) contains approximately 4.0 grams of absolute ethanol.

4.8 UNDESIRABLE EFFECTS

Clinical studies

Monotherapy

Breast, non small cell lung and ovarian cancer

The adverse reactions 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^2 without the recommended premedication, and from 2106 (2045 with normal* and 61 with elevated* LFTs at baseline) patients who received an initially planned dose of 100 mg/m^2 over a one hour infusion every 3

weeks independently of the pre-medication. 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 tumour types).

The safety profile is generally similar between patients receiving docetaxel for the treatment of breast, non small cell lung or ovarian carcinoma.

The following table lists the adverse reactions data:

Table 2: Summary of adverse events in patients receiving docetaxel at 75 and 100 mg/m² as a single agent

	Normal LFTs* at Baseline		**Elevated LFTs* at Baseline**
Docetaxel dosage	**75 mg/m²**	**100 mg/m²**	**100 mg/m²**
Number of patients	**n =75** **%**	**n=2045** **%**	**n=61** **%**
Haematological Toxicity			
Neutropenia			
ANC~ <2.0 cells x 10^9/L	-	95.5	96.4
ANC~ <0.5 cells x 10^9/L	73.0	75.4	87.5
Febrile neutropenia (fever/ANC~ <0.5 x 10^9/L):			
by patient	-	11.0	26.2
by cycle	-	2.6*	8.7
(fever/ANC~ <1 x 10^9/L):			
by patient	5.0	-	-
by cycle	1.5	-	-
Thrombocytopenia			
<100 cells x 10^9/L	6.7	8.0	24.6
Anaemia			
<110 g/L	86.7	90.4	91.8
<80 g/L	9.0	8.8	31.1
Non-Haematological 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

	Normal LFTs* at Baseline		Elevated LFTs* at Baseline
Docetaxel dosage	**75 mg/m^2**	**100 mg/m^2**	**100 mg/m^2**
Number of patients	**n =75 %**	**n=2045 %**	**n=61 %**
Cutaneous			
Skin:			
All	45.3	47.6	54.1
Severe	1.3	4.8	9.8
Nail Disorder	50.0	30.6	23.0
Alopecia	92.0	75.8	62.3
Gastrointestinal			
Nausea	44.0	38.9	37.7
Diarrhoea	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	--	--
Infusion site reactions consisting of hyperpigmentation, inflammation, redness or dryness of skin, phlebitis or extravasation and swelling of vein	5.6	4.4	3.3

* Normal liver function tests (LFTs): transaminase ≤1.5 times upper limit of normal or alkaline phosphatase ≤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 2045 patients with normal baseline liver function tests treated with docetaxel as monotherapy at the initially planned dose of 100 mg/m^2. 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 occur 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, dyspnoea and drug fever or chills (see **Section 4.4 Special Warnings and Precautions for Use**).

Haematological

Bone marrow suppression and other haematologic adverse reactions to docetaxel include:

Neutropenia (in patients who did not receive G-CSF), the most frequent adverse reactions, was reversible and not cumulative. The median day to nadir was 7 days and the median duration of severe neutropenia was 7 days.

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

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

Neurological

Mild to moderate neuro-sensory signs and/or symptoms occurred in 50% of the patients. Severe neurosensory symptoms (paraesthesia, 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) mainly characterised 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^2 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 reaction profile is consistent with the known toxicities of monotherapy treatments.

The most frequent treatment-related adverse reactions (≥ 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 the table below.

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 reactions. The percentages of patients requiring dose reductions due to adverse reactions were 65% in the combination arm and 36% in the monotherapy arm.

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

	Capecitabine 1250 mg/m^2 twice daily with docetaxel 75 mg/m^2/3 weeks (n=251)		**Docetaxel 100 mg/m^2/3 weeks (n-255)**	
Body System	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse reaction	%	%	%	%
Gastrointestinal				
Stomatitis	67	18	42	5
Diarrhoea	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	-
Cutaneous				
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
Oncholysis	5	1	5	1
General				
Asthenia	23	3	22	5
Pyrexia	21	1	29	<1
Fatigue	21	4	25	5

	Capecitabine 1250 mg/m^2 twice daily with docetaxel 75 mg/m^2/3 weeks (n=251)		Docetaxel 100 mg/m^2/3 weeks (n-255)	
Body System	All Grades	Grade 3/4	All Grades	Grade 3/4
Adverse reaction	%	%	%	%
Weakness	13	1	9	2
Pain in limb	9	<1	8	<1
Lethargy	6	-	5	1
Pain	6	-	2	-
Neurologic				
Taste disturbance	15	<1	14	<1
Paraesthesia	11	<1	15	1
Dizziness	9	-	6	<1
Headache	7	<1	8	1
Peripheral Neuropathy	5	-	10	1
Cardiovascular				
Lower limb oedema	14	1	12	1
Sore throat	11	2	7	<1
Dyspnoea	7	1	9	<1
Cough	6	<1	9	-
Epistaxis	5	<1	5	-
Metabolism				
Anorexia	12	1	10	1
Decreased appetite	10	-	4	-
Dehydration	8	2	5	1
Decreased weight	6	-	4	-
Eye				
Increased lacrimation	12	-	5	-
Musculoskeletal				
Myalgia	14	2	24	2
Anthralgia	11	1	18	2
Back pain	7	1	6	1
Infection				
Oral candidiasis	6	<1	7	<1
Haematologic*				
Decreased haemoglobin	13	4	11	4
Neutropenic fever	21	16	21	21
Leukopenia	3	3	2	2
Biochemical laboratory abnormalities*				
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

Adverse Event	**Capecitabine with Docetaxel (n=251)**
Laboratory Abnormalities	Grade 3/4 %
Neutropenia	63

Adverse Event	Capecitabine with Docetaxel (n=251)
Anaemia	10
Thrombocytopenia	3
Hyperbilirubinemia	9

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

Combination with trastuzumab (HER 2+)

The table below displays adverse events (all Grades) which were reported in ≥10% of patients treated with docetaxel in combination with trastuzumab for metastatic breast cancer.

Table 5

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
	lymphoedema	11
Gastrointestinal disorders	nausea	45
	diarrhoea	43
	vomiting	29
	constipation	27
	stomatitis	20
	dyspepsia	14
	abdominal pain	12
Nervous system disorders	paraesthesia	32
	headache	21
	dysgeusia	14
	hypoaesthesia	11
Blood and lymphatic system disorders	neutropenia	33
	febrile neutropenia	20
	anaemia	15
	leukopenia	12
Musculoskeletal and connective tissue disorders	myalgia	27
	arthralgia	27
	pain in extremity	16

Body System	Adverse Event	Docetaxel plus Trastuzumab N=92 (%)
	bone pain	14
	back pain	11
Respiratory, thoracic and mediastinal disorders	epistaxis	20
	pharyngolaryngeal pain	16
	nasopharyngitis	15
	dyspnoea	14
	cough	13
	rhinorrhoea	12
Eye disorders	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]

	Docetaxel plus Trastuzumab N=92	Docetaxel N=94
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.

Haematological 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^2 every 3 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

	Docetaxel 75 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 n=744		Fluorouracil 500 mg/m^2 + Doxorubicin 50 mg/m^2 + Cyclophosphamide 500 mg/m^2 n=736	
Body System	Any	Grade 3/4	Any	Grade 3/4
Adverse Event	(%)	(%)	(%)	(%)
Cutaneous				

	Docetaxel 75 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² n=744		**Fluorouracil 500 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² n=736**	
Body System	Any	Grade 3/4	Any	Grade 3/4
Adverse Event	(%)	(%)	(%)	(%)
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
Haematologic				
Anaemia	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
Gastrointestinal				
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
Diarrhoea	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
General				
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 oedema	26.7	0.4	7.2	0.0
Hypersensitivity reactions	10.5	1.1	2.2	0.0
Lymphoedema	0.3	0.0	0.0	0.0
Gynaecologic				
Amenorrhoea	57.6	N/A	48.1	N/A
Neurologic				
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
Musculoskeletal				
Myalgia	22.8	0.8	8.0	0.0
Anthralgia	15.1	0.4	5.7	0.3
Cardiovascular				
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
Metabolic				

	Docetaxel 75 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² n=744		Fluorouracil 500 mg/m² + Doxorubicin 50 mg/m² + Cyclophosphamide 500 mg/m² n=736	
Body System	Any	Grade 3/4	Any	Grade 3/4
Adverse Event	(%)	(%)	(%)	(%)
Anorexia	19.9	2.2	16.4	1.2
Weight gain or loss	15.2	0.3	9.2	0.0
Eye				
Lacrimation disorder	9.8	0.1	6.4	0.0
Conjunctivitis	4.6	0.3	6.0	0.1
Respiratory				
Cough	3.1	0.0	2.2	0.1

N/A not applicable
* there was no specific death in either treatment arms
** one patient died due to heart failure in TAC arm

Of the 744 patients treated with TAC, 33.1% experienced severe TEAEs. Dose reductions due to haematological toxicity occurred in 1% of cycles in TAC arm. Six percent 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 during the study period.

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 leukaemia/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, asthenia, amenorrhoea, neurosensory and peripheral oedema. Among the adverse events that persisted into the follow-up period in > 1% of patients, the majority of events resolved; however, amenorrhoea, and lymphoedema remained ongoing in TAC patients.

Combination with doxorubicin and 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 ≥ 5% for non-cardiac AEs; incidence of ≥ 1% for cardiac AEs)

	AC-T n=1050		AC-TH n=1068		TCH n=1056	
Adverse Event	**Overall**	**Grade 3/4**	**Overall**	**Grade 3/4**	**Overall**	**Grade 3/4**
(NCI-CTC term)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Alopecia	1029 (98.0)	0	1047 (98.0)	0	1012 (95.8)	0
Haemoglobin[a]	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)
Leucocytes[a]	878 (83.6)	540 (51.4)	929 (87.0)	643 (60.2)	877 (83.0)	507 (48.0)
Neutrophils[a]	859 (81.8)	664 (63.2)	922 (86.3)	761 (71.3)	859 (81.3)	696 (65.9)
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)[a]	506 (48.2)	7 (0.7)	579 (54.2)	19 (1.8)	561 (53.1)	25 (2.4)
Fluid retention[a,b]	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)
Diarrhoea	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)[a]	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[a]	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[a]	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)
Dyspnoea	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[c]	98 (9.3)	4 (0.4)	86 (8.1)	4 (0.4)	57 (5.4)	0

	AC-T n=1050		AC-TH n=1068		TCH n=1056	
Adverse Event	**Overall**	**Grade 3/4**	**Overall**	**Grade 3/4**	**Overall**	**Grade 3/4**
(NCI-CTC term)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
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[a]	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[c]	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[a]	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)
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.

a = Regardless of causality
b = Fluid retention AEs are defined as "oedema only", or "weight gain only", or "lung oedema only", or "oedema and weight gain", or "oedema and lung oedema", or "oedema + weight gain + lung oedema". "Fluid retention" corresponds to the NCI-CTC term "oedema".
c = COSTART term

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, Clinical trials**). 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. AC was associated with more nausea and vomiting (all grades as well as grades 3 and 4). But TC had more low-grade oedema, 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**
Haematologic								
Anaemia	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
Nonhaematological								
Asthenia	43	32	3	<1	42	31	4	<1
Oedema	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
*COSTART term

Prostate cancer

Combination with prednisone or prednisolone

The adverse reaction profile is consistent with the known safety profile of docetaxel.

The table below provides the percentage of subjects with clinically important treatment-emergent adverse events (TEAEs) and haematological toxicities related to study treatment, reported in the phase III clinical trial for docetaxel 75 mg/m^2 q3w 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^2 every 3 weeks (n=332) %		Mitozantrone 12 mg/ m^2 every 3 weeks (n=335) %	
	Grade 3/4	**Any**	**Grade 3/4**	**Any**
Cutaneous				
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
Haematologic				
Neutropenia	32.0	40.9	21.7	48.2
Anaemia	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
General				
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
Gastrointestinal				
Nausea	2.4	35.5	0.9	28.7
Diarrhoea	1.2	24.1	0.9	4.2
Vomiting	1.2	13.3	0.6	7.2

	Docetaxel 75 mg/m^2 every 3 weeks (n=332) %		Mitozantrone 12 mg/ m^2 every 3 weeks (n=335) %	
Neurologic				
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
Respiratory				
Dyspnoea	0.6	4.5	0.3	3.3
Cough	0.0	1.2	0.0	0.9
Eye				
Tearing	0.6	9.3	0.0	1.5
Musculoskeletal				
Myalgia	0.3	6.9	0.0	3.3
Arthralgia	0.3	3.0	0.0	0.6
Cardiovascular				
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

The following table summarises the safety data obtained in 174 patients (TAX 323) and 251 patients (TAX 324) with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who were treated with docetaxel 75 mg/m^2 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

	TAX323: docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 (n=174)		TAX324: docetaxel 75 mg/m^2 + cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 (n=251)	
Adverse Event	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Blood and lymphatic system				
Neutropenia	93.1	76.3	94.8	83.5
Anaemia	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	N/A
Febrile neutropenia*	5.2	0.0	12.1	N/A
Allergy	2.9	0.0	0.4	0.0
Skin and subcutaneous tissue disorders				
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
Fluid retention	20.1	0.0	13.1	1.2
Oedema only	12.6	0.0	12.0	1.2
Weight gain only	5.7	0.0	0.4	0.0
Gastrointestinal disorders				
Nausea	43.7	0.6	75.7	13.9
Stomatitis	42.0	4.0	64.5	20.7

	TAX323: docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 + fluorouracil 750 mg/m^2 (n=174)		TAX324: docetaxel 75 mg/m^2 + cisplatin 100 mg/m^2 + fluorouracil 1000 mg/m^2 (n=251)	
Adverse Event	**Any %**	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Diarrhoea	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
Oesophagitis/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
Nervous system disorders				
Neurosensory	16.7	0.6	11.6	1.2
Neuromotor	-	-	7.2	0.4
Dizziness	1.1	-	9.6	2.0
Cardiac disorders				
Myocardial Ischemia	1.7	1.7	0.8	0.8
Cardiac dysrhythmia	0.6	0.6	3.2	0.2
Vascular disorder				
Venous	1.1	0.6	0.8	0.4
Metabolism and nutrition disorders				
Anorexia	15.5	0.6	37.8	12.0
Weight loss	9.8	0	11.2	0.0
Eye disorders				
Tearing	1.7	0	1.6	0.0
Conjunctivitis	1.1	0	0.8	0.0
Ear and labyrinth disorders				
Altered hearing	5.7	0	11.2	1.2
Musculoskeletal, connective tissue and bone disorders				
Myalgia	6.3	0.6	5.2	0.4
General disorders and administration site conditions				
Lethargy	37.9	3.4	58.6	4.0
Cancer pain	1.1	0.6	3.2	1.2

* Febrile neutropenia: Grade ≥2 fever concomitant with Grade 4 neutropenia requiring i.v. antibiotics and/or hospitalisation
Clinically important TEAEs were determined based upon frequency, severity, and clinical impact of the adverse event

Post marketing reactions

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 ≥ 1-10%, uncommon 0.1-1%; rare 0.01-0.1%; 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: anaphylactic shock resulted in a fatal outcome in patients who received premedication.

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

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

Cutaneous

Very rare: cases of cutaneous lupus erythematous 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 characterised by hypo- or hyperpigmentation, and infrequently onycholysis and pain.

Acute generalized exanthematous pustulosis has been reported.

Fluid retention

Rare: dehydration and pulmonary oedema have been reported.

Gastrointestinal

Rare: constipation, oesophagitis and taste perversion, ileus and intestinal obstruction, gastrointestinal perforation, neutropenic enterocolitis[a], colitis[a] including ischemic colitis[a], gastrointestinal haemorrhage, dehydration as a consequence of gastrointestinal events.
Very rare: duodenal ulcer.

[a] 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[b], congestive heart failure.
Rare: atrial fibrillation, syncope, tachycardia[b].
Very rare: myocardial infarction, deep vein thrombosis, ECG abnormalities, thrombophlebitis, pulmonary embolism.

Vein disorder, venous thromboembolism and haemorrhage have been reported.

[b] In post-marketing,ventricular arrhythmia including ventricular tachycardia has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 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, have 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 anti-tumour 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 Oedema (CMO) have been reported in patients treated with docetaxel, as well as with other taxanes.

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea.
Rare: Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, acute pulmonary oedema, pulmonary fibrosis, respiratory failure, and radiation recall phenomena have rarely been reported, and may be associated with fatal outcome. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant therapy.

Respiratory failure has been reported.

Musculoskeletal and connective tissue disorders

Myositis has been reported.

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.

Blood and lymphatic disorders

Very rare: cases of acute myeloid leukaemia 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.

Renal and urinary disorders

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

Other

Common: generalised or localised pain including chest pain without cardiac or respiratory involvement.

Metabolism and nutrition disorders

Tumour lysis syndrome has been reported. Cases of electrolyte imbalance have been reported. Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia. Hypokalaemia, hypomagnesaemia and hypocalcaemia were observed, usually in association with gastrointestinal disorders and in particular diarrhoea.

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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

OVERDOSE

Symptoms

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

Treatment

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

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.

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.

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 75 mg/m^2 dose in 55 previously untreated patients and 100 mg/m^2 in 117 previously untreated and 111 previously treated patients. In these trials, docetaxel was administered as a one-hour infusion every 3 weeks.

Patients treated at 75 mg/m^2

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) was 47% with 9% complete responses (CR). 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 ≤ 2 organs involved, the response rate was 58.6% and in patients with ≥ 3 organs involved 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/m²

Phase II trials

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) was 56% with 9.4% complete responses (CR). The ORR was 48.6% with 3.6% CR in the previously treated population including 48.2% ORR with 3.6% CR 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^2 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 pretreated patients and 53.1% in the subgroup of 49 anthracycline resistant patients).

In patients with ≥ 3 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, 63.6% in previously treated and 63.2% in the subgroup of anthracycline resistant patients).

Phase III trials

Two randomised 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^2 administered every 3 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^2 every 3 weeks) on intent-to-treat and evaluable patient analyses. 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 months; 95% 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 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^2 every 6 weeks and 6 mg/m^2 every 3 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, multicentre, randomised 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 randomised to receive docetaxel 100 mg/m^2 as a one-hour infusion or paclitaxel 175 mg/m^2 as a 3-hour infusion. Both regimes were administered every 3 weeks. Efficacy results are described in the following table.

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^2 n=225	paclitaxel 175 mg/m^2 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, neurologic 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, multicentre, randomised 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 randomised to receive capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1 week rest period) in combination with docetaxel (75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks). 256 patients received docetaxel 100 mg/m^2 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 below. Health related quality of life (HRQoL) was assessed using the European Organisation 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[1]

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[2]=0.643 [0.563, 0.770]	 0.0001
Survival median [95% CI]	418 days [374, 492]	338 days [298, 362]	HR[2]=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

1. All-randomised population, Investigator assessment
2. Hazard Ratio

Combination with trastuzumab (HER2+)

Docetaxel in combination with trastuzumab was studied for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2, and who previously had not received chemotherapy for metastatic disease. One hundred and eighty-six patients received docetaxel (100 mg/m^2) 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* hybridisation (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 summarised in table below.

Table 14: Efficacy Outcomes in Docetaxel + Trastuzumab Combination Therapy

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

1 Full analysis set (intent-to-treat) 2 Estimated median survival
*p log-rank test **p Chi-square test
TTP time to progression 'ne' indicates that it could not be estimated or it was not yet reached

Adjuvant treatment of breast cancer

Combination with doxorubicin and cyclophosphamide

Data from a multicentre open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with node-positive breast cancer and KPS ≥ 80%, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either docetaxel 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1 hour infusion, all other drugs were given as IV 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^2. Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally b.i.d. for 10 days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive oestrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 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 (0.59-0.88), 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 (0.53-0.91), 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 (TAX316), docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater.

The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

TAC-treated patient subsets according to prospectively defined major prognostic factors were analysed:

Table 15: Analysis of TAC-treated patient subsets

		Disease Free Survival			Overall Survival		
Patient subset	Number of patients	Hazard ratio*	95% CI	P=	Hazard ratio*	95% CI	P=
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.070	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
Hormone Receptor status							
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
Her-2-neu status							
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 tumours overexpress HER2 (with node positive and high risk node negative). A total of 3,222 women were randomised in the study, and 3,174 were treated with either: AC-T, AC-TH, or TCH.

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

- AC-TH: Doxorubicin 60 mg/m^2 IV in combination with cyclophosphamide 600 mg/m^2 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^2 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^2 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 summarised in the following table.

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	AC-TH	TCH	AC-T	AC-TH	TCH
	n=1073	n=1074	n=1075	n=1073	n=1074	n=1075
Stratified analysis						
Hazard ratio[a]	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)
p-value[b]	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[c]		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-H=doxorubicin plus cyclophosphamide, followed by docetaxel in combination with trastuzumab; TCH=Docetaxel in combination with trastuzumab and carboplatin.
CI=confidence interval; NA=not applicable.
a=Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status.
b=Stratified log-rank p-value.
c=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.

Table 17: Disease Free Survival (Intent to Treat Population) according to Nodal Status

	High risk node-negative patients			**Node positive patients**		
	AC-T	AC-TH	TCH	AC-T	AC-TH	TCH
	n=309	n=306	n=307	n=764	n=768	n=768
Stratified analysis						
Hazard ratio[a]	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[b]	NA	0.0010	0.0209	NA	0.0008	0.0029
Percent event free at 3 years (95% CI)	88.0% (84.1-97.8%)	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[c]		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.
a=Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status.
b=Stratified log-rank p-value.
c=Absolute benefit in percent event free compared to AC-T.

Combination with cyclophosphamide

Docetaxel in combination with cyclophosphamide (TC) was investigated in a phase III randomised 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^2 respectively every three weeks; n=510), or four cycles of TC (75 mg and 600 mg/m^2 every three weeks; n=506) as adjuvant chemotherapy after complete surgical excision of the primary tumour. Patients had to have a primary tumour of ≥ 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% Cl 0.50 to 0.94 p=0.015).

Non small cell lung cancer

Patients treated at 75 mg/m^2

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 75 mg/m^2 dose given as a one-hour infusion every 3 weeks. The response rate was 10%.

Patients treated at 100 mg/m^2

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 100 mg/m^2 dose given as a one-hour infusion every 3 weeks.

The 100 mg/m^2 dose is associated with higher toxicity.

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) 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 9 and 8 months, respectively.

Ovarian cancer

Patients treated at 100 mg/m^2

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^2 in a one hour intravenous infusion every three weeks.

In 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 randomised multicentre Phase III trial. A total of 1006 patients with KPS ≥ 60 were randomised to the following treatment groups:

- Docetaxel 75 mg/m^2 every 3 weeks for 10 cycles.
- Docetaxel 30 mg/m^2 administered weekly for the first 5 weeks in a 6 week cycle for 5 cycles.
- Mitozantrone 12 mg/m^2 every 3 weeks for 10 cycles.

All 3 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 3 weekly arm versus the control arm are summarised in the following table.

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+*	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
Tumour response rate (%)	12.1	6.6
95% CI	(7.2-18.6)	(3.0-12.1)
p-value*	0.1112	-

+ stratified log rank test
* threshold for statistical significance=0.0175
** PSA: Prostate-Specific Antigen

Head and neck cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicentre, open-label, randomised trial (TAX 323). In this study, 358 previously untreated patients with locally advanced inoperable stage III/IV SCCHN, and WHO performance status 0 or 1, were randomised to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 on Day 1, followed by fluorouracil (F) 750 mg/m^2 per day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin 100 mg/m^2 on Day 1, followed by fluorouracil 1000 mg/m^2 (PF) as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional guidelines (PF/RT). At the end of chemotherapy, with a minimal interval

of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines.

Conventional locoregional radiotherapy was given to approximately 77% of the patients at a total dose of 66 - 70 Gy (1.8 Gy - 2.0 Gy once a day, 5 days per week) while accelerated/hyperfractionated regimens of radiation therapy were used in approximately 23% of patients (twice a day, with a minimum interfraction interval of 6 hours, 5 days per 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 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival was significantly longer in favour of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, p=0.0128. Patients with tumours of the nasopharynx and the nasal/paranasal cavities were excluded from this study. Efficacy results are presented in the table below.

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)	67.8 (60.4 – 74.6)	53.6 (46.0 – 61.0)
***p-value	0.006	
Overall response rate to study treatment [chemo- ± radio-therapy (%) (95% CI)	72.3 (65.1 – 78.8)	58.6 (51.0 – 65.8)
***p-value	0.006	
Median duration of response to chemo- ± radio-therapy (months) (95% CI)	n=128 15.7 (13.4 – 24.6)	n=106 11.7 (10.2 – 17.4)
Hazard Ratio (95% CI) **p-value	0.72 (0.52 – 0.99) 0.0457	

A Hazard Ratio of less than 1 favours Docetaxel + Cisplatin + FU
*Cox model (adjustment for Primary tumour site, T and N clinical stages and PSWHO)
**Logrank 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 favour 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 - 21.0 months) compared to PF (8.3 months; 95% CI: 7.3 - 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 - 1.41). There was no difference in pain intensity in patients treated with TPF or PF.

Induction chemotherapy followed by chemoradiotherapy (TAX324)

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 randomised, multicentre open-label, phase III trial (TAX324). Patients with tumours 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 randomised to one of two arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m^2 by IV infusion on day 1, followed by cisplatin (P) 100 mg/m^2 administered as a 30 minute to three hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m^2/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 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^2 administered as a 30 minute to three hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m^2/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 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 7 weeks of CRT following induction chemotherapy with a minimum interval of 3 weeks and no later than 8 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 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks, for a total dose of 70 - 72 Gy). Surgery on the primary site of disease and/or neck could be considered at any time following completion of CRT.

The primary efficacy endpoint in this study, overall survival (OS) was significantly longer (log-rank test p=0.0058) with the docetaxel-containing regimen compared to PF (median OS: 70.6 vs 30.1 months, respectively), with a 30% risk reduction in mortality compared to PF (hazard ratio (HR)= 0.70, 95% confidence interval (CI)= 0.54 - 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 - 0.90; log-rank test p=0.004. Efficacy results are presented in table below.

Table 20: Efficacy of docetaxel in the induction treatment followed by chemoradiotherapy for patients with locally advanced SCCHN (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)	71.8 (65.8 – 77.2)	64.2 (57.9 – 70.2)

Endpoint	Docetaxel + Cis + FU n=255	Cis + FU n=246
***p-value	0.070	
Best overall response (CR + PR) to study treatment [induction chemotherapy ± chemoradiotherapy] (%) (95% CI)	76.5 (70.8 – 81.5)	71.5 (65.5 – 77.1)
***p-value	0.209	

A Hazard Ratio of less than 1 favours 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

No data available.

Distribution

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5-115 mg/m^2 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 α, β and γ 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^2 dose given as a one-hour infusion a mean peak plasma level of 3.7 µg/mL was obtained with a corresponding AUC of 4.6 h.µg/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m^2 and 113 L, respectively.

Metabolism

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 ≥ 1.5 times the upper limit of normal associated with alkaline phosphatase ≥ 2.5 times the upper limit of normal), total clearance was lowered by on average 27% (see **Section 4.2 Dose and Method of Administration**). Docetaxel clearance was not modified in patients with mild to moderate fluid retention. No data is 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_{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 tumours had no influence on the pharmacokinetics of each individual drug.

Excretion

A study of ^{14}C-docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and faeces following oxidative metabolism of the tert-butyl ester group, within seven days, the

urinary and faecal excretion account for about 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity (60% of the administered dose) recovered in faeces is excreted during the first 48 hours as one major and three minor inactive metabolites and very low amounts of unchanged drug.

5.3 PRECLINICAL SAFETY DATA

Preclinical data

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour 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 over expressing the *p*-glycoprotein, which is encoded by the multidrug resistance gene. *In vivo,* docetaxel is schedule independent and has a broad spectrum of experimental antitumour activity against advanced murine and human grafted tumours. Against transplantable murine tumours *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 was mutagenic in the *in vitro* chromosome aberration assay, in the *in vivo* micronucleus test in the mouse and modified the distribution of CHO-K1 cells in the cell cycle phases.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Citric acid

Absolute ethanol

Polysorbate 80.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C and protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Docetaxel Accord is supplied in single-dose Type I glass vials with a fluorotec plus rubber stopper and flip-off seal.

Three strengths are available containing docetaxel as follows:

20 mg/1 mL

80 mg/4 mL and

160 mg/8 mL

In packs of 1.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Docetaxel is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing docetaxel solutions. Procedures for proper handling and disposal of anticancer drugs should be applied. The use of gloves is recommended.

If docetaxel concentrate or infusion solution comes into contact with the skin, wash immediately and thoroughly with soap and water. If docetaxel concentrate or infusion solution comes into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation and storage of the infusion solution

Docetaxel concentrated injection is for single use in one patient only. Discard any unused residue.

More than one concentrate vial may be necessary to obtain the required dose for the patient.

Based on required dose for the patient expressed in mg, using a 21 gauge needle, aseptically withdraw the corresponding volume of Docetaxel Concentrate solution (20 mg/mL) from the appropriate number of concentrate vials using a single calibrated syringe fitted with a needle [For example a dose of 140 mg docetaxel would require 7 mL of docetaxel concentrate solution]. Inject the required concentrate volume via a single injection (one shot) into a 250 mL infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded. Mix the infusion bag or bottle manually using a rocking motion.

Note: The one shot technique reduces the number of needle insertions into the infusion bag hence minimising the risk of crystallisation.

Although chemical and physical stability of the diluted docetaxel solution for infusion prepared as recommended in 0.9% sodium chloride and 5% glucose solution in non-PVC bags has been demonstrated for up to 6 hours at 20 - 25°C and for 24 hours when stored between 2 - 8°C, the product contains no antimicrobial preservative.

To reduce microbiological hazard and crystallization of docetaxel, use as soon as practicable after dilution. If storage is necessary, hold at 2 - 8°C for not more than 24 hours (including the time to allow the infusion solution to return to room temperature before infusion).

Docetaxel infusion solution is supersaturated, therefore may crystallise over time. If crystals appear, the solution must no longer be used and should be discarded.

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland 2022
New Zealand

Phone: 0800 004 375

9 DATE OF FIRST APPROVAL

12 August 2021

10 DATE OF REVISION

14 November 2023

Version 4.0

Summary table of changes

Section Changed	Summary of new information
Throughout	Editorial changes
4.2	Added sub-heading under Prostate cancer. Added narrative to Table 1. Added the following sections; “Use in renal impairment”, “Dialysis”, “Concomitant disease”, and “Maximum tolerated daily and the maximum dose for an entire course of therapy”.
4.4	Updated Haematology section, Gastrointestinal reactions section
4.6	Updated “Effects on fertility” Updated “Use in pregnancy” and “Use in lactation”. Added “Contraception in males and females”
4.7	Added refrain from driving until effect is known.
4.8	Updated “Respiratory, thoracic and mediastinal disorders”.