

DATA SHEET

1 PRODUCT NAME

Taxotere 40mg/mL concentrate for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TAXOTERE Concentrated Injection and Diluent

Single-dose vials of TAXOTERE concentrated injection containing 20 or 80mg of docetaxel (anhydrous), in 0.5 or 2.0mL polysorbate 80, respectively. The sterile pyrogen-free viscous solution contains 40mg/mL docetaxel (anhydrous).

Each mL of docetaxel solution contains 40mg docetaxel anhydrous and 1040mg polysorbate 80.

The corresponding vials of diluent for TAXOTERE 20mg and 80mg concentrated injections contain 1.98 and 7.33mL of ethanol, respectively in water for injections.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

TAXOTERE concentrate for infusion to be diluted is supplied in single-dose vials as a sterile pyrogen-free non-aqueous clear yellow to brown yellow viscous solution with the accompanying sterile solvent (13% ethanol in water for injections).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Breast Cancer

Metastatic Breast Cancer

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

TAXOTERE 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.

Adjuvant Treatment of Breast Cancer

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

Doxorubicin and cyclophosphamide followed by TAXOTERE in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

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

Non Small Cell Lung Cancer

TAXOTERE 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.

Prostate Cancer

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

Head and Neck Cancer

TAXOTERE, in combination with cisplatin and fluorouracil is indicated in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

4.2 DOSE AND METHOD OF ADMINISTRATION

Breast Cancer

Metastatic Breast Cancer

Monotherapy

The recommended dosage of TAXOTERE is 75 to 100mg/m² administered as a one-hour infusion every three weeks (see **section 6.6 Preparation for the Intravenous Administration**). A dose of 100mg/m² has been shown to result in a moderate increase in response rates compared with 75mg/m² but is associated with greater toxicity.

Combination with Capecitabine

The recommended dosage of TAXOTERE is 75mg/m² administered as a one-hour infusion every three weeks when combined with capecitabine administered orally at 1,250mg/m² 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.

Adjuvant Treatment of Breast Cancer

Combination with Doxorubicin and Cyclophosphamide

The recommended dose of TAXOTERE in the adjuvant treatment of breast cancer is 75mg/m² administered 1 hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² every 3 weeks for a total of six cycles (see also **section 4.2 Dosage Adjustments During Treatment** and **section 4.4, Haematology**).

Combination with Trastuzumab following Doxorubicin and Cyclophosphamide (HER2+)

- AC-TH:

AC (cycles 1 – 4): doxorubicin (A) 60 mg/m² followed by cyclophosphamide (C) 600 mg/m² administered every three weeks for 4 cycles.

TH (cycles 5 – 8): docetaxel (T) 100 mg/m² 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/m²

Days 8 and 15: trastuzumab 2 mg/kg

- Cycles 6 – 8:

Day 1: docetaxel 100 mg/m² 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/m² 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/m² 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/m² 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.

Non Small Cell Lung Cancer

The recommended dosage of TAXOTERE is 75 to 100mg/m² administered as a one-hour infusion every three weeks (see **section 6.6 Preparation for the Intravenous Administration**). A dose of 100mg/m² has been shown to result in a moderate increase in response rates compared with 75mg/m² but is associated with greater toxicity.

Prostate Cancer

The recommended dosage of TAXOTERE for prostate cancer is 75mg/m² administered as a one-hour infusion every three weeks. Prednisone or prednisolone 5mg 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 TAXOTERE is 75mg/m² as a one hour infusion followed by cisplatin 75mg/m² over one hour, on day one, followed by fluorouracil as a continuous infusion at 750mg/m² 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 TAXOTERE is 75mg/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100mg/m² administered as a 30 minute to 3 hour infusion, followed by fluorouracil 1000mg/m² 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, and Head and Neck Cancers

A premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg 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 8mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion.

Dosage Adjustments During Treatment

TAXOTERE should be administered when the neutrophil count is ≥ 1.5 cells $\times 10^9/L$.

In Patients Treated at 75mg/m²

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells $\times 10^9/L$ for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 75mg/m² to 55mg/m² (or to 60mg/m² for adjuvant therapy for breast cancer). If the patient continues to experience these reactions at 55mg/m² (or at 60mg/m²), the treatment should be discontinued.

In Patients Treated at 100mg/m²

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells $\times 10^9/L$ for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during TAXOTERE therapy should have the dosage of TAXOTERE reduced from 100mg/m² to 75mg/m². If the patient continues to experience these reactions at 75mg/m², the dosage should either be decreased from 75mg/m² to 55mg/m², or the treatment should be discontinued.

Patients Treated with TAXOTERE in Combination with Capecitabine

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

For patients developing the first appearance of a Grade 2 toxicity which persists at the time of the next TAXOTERE/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 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 TAXOTERE 55mg/m².

For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the TAXOTERE dose.

Patients Treated with TAXOTERE in Combination with Doxorubicin and Cyclophosphamide (TAC)

In the TAXOTERE, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow-up (see **section 4.8**).

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 this reaction should remain on G-CSF and have their TAXOTERE dose reduced to 60mg/m². If G-CSF is not used, the TAXOTERE dose should be reduced from 75 to 60mg/m². Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m².

Patients Treated with TAXOTERE 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 TAXOTERE will be reduced from 100 mg/m² to 75 mg/m² (in the AC-TH regimen); TAXOTERE will be reduced from 75 mg/m² to 60 mg/m² (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 TAXOTERE in Combination with Cisplatin and Fluorouracil in Head and Neck cancer

Patients treated with TAXOTERE 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 TAXOTERE dose should be reduced from 75 to 60 mg/m². If subsequent episodes of complicated neutropenia occur the TAXOTERE dose should be reduced from 60 to 45 mg/m².

In case of Grade 4 thrombocytopenia the TAXOTERE dose should be reduced from 75 to 60 mg/m². Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level > 100 000 cells/m³. 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 TAXOTERE in Combination with cisplatin and fluorouracil

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

Special Populations

Patients with Hepatic Impairment

In Patients Treated at 75mg/m²

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 100mg/m²

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 75mg/m² (see **section 5.2 Pharmacokinetics**). 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.

Children

The safety and effectiveness of TAXOTERE 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 TAXOTERE, see capecitabine Product Information.

For instructions on safe handling and preparation before administration see **section 6.6**.

4.3 CONTRAINDICATION

TAXOTERE is contraindicated in patients who have a history of severe hypersensitivity reactions to TAXOTERE or polysorbate 80.

TAXOTERE should not be used in patients with baseline neutrophil count of <1.5 cells x 10⁹/L.

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

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of TAXOTERE 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 TAXOTERE administration. A premedication consisting of an oral corticosteroid such as dexamethasone 16mg per day (e.g. 8mg twice daily) for 3 days starting one day prior to TAXOTERE 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**)

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

Haematology

Bone marrow suppression and other haematologic effects to TAXOTERE include neutropenia, the most frequent adverse reaction of TAXOTERE (see **section 4.8, 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 $\times 10^9/L$.

TAXOTERE should not be administered to patients with baseline neutrophil counts of less than <1.5 cells $\times 10^9/L$. Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel. Patients should not be retreated with TAXOTERE until neutrophils recover to a level ≥ 1.5 cells $\times 10^9/L$. (see **section 4.2**).

In the case of severe neutropenia (<0.5 cells $\times 10^9/L$ for seven days or more) during a course of TAXOTERE 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 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 this reaction should remain on G-CSF and have their TAXOTERE dose reduced (see also **Dosage Adjustments During Treatment**).

In the treatment of adjuvant breast cancer, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow-up (see **section 4.8**).

Gastrointestinal Reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. 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 (see **section 4.2, 4.4 Haematology, 4.8**).

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 TAXOTERE, 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, fatal anaphylaxis (very rarely) or generalised rash/erythema require immediate discontinuation of TAXOTERE 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 TAXOTERE.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a potentially fatal hypersensitivity reaction to TAXOTERE.

Cutaneous Reactions

Reversible cutaneous reactions were generally mild to moderate. Reactions were characterised by a rash including localised eruptions with oedema 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, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes have been reported with docetaxel. 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 16mg per day (e.g. 8mg 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**).

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 75mg/m² is 524mg/m² and treatment at 100mg/m² is 509mg/m² (without premedication) and 797mg/m² (with premedication). Fluid retention is slowly reversible after docetaxel treatment is stopped. In patients treated by docetaxel as single agent, at 100mg/m²,

the median cumulative dose to treatment discontinuation was more than 1,000 mg/m² 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 with Liver Impairment

Liver function tests (LFTs) should be measured at baseline and before each cycle.

In patients treated with docetaxel at 100mg/m² who have both elevations of serum transaminase values (ALT and/or AST) greater than 1.5 times the upper limit of normal (ULN) and increases in alkaline phosphatase greater than 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 75mg/m² (see **section 4.2**).

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 TAXOTERE should be taken into account when given to patients with hepatic impairment (see **section 6.5**).

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**).

The amount of ethanol in TAXOTERE should be taken into account when given to patients with epilepsy (see **section 6.5**).

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

Cardiac Toxicity

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

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**).

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

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.

Leukaemia

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

Use in the Elderly

An analysis of safety data in patients equal to or greater than 60 years of age treated with TAXOTERE 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.

Of the 333 patients treated with TAXOTERE every three weeks 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 TAXOTERE every three weeks, the incidence of anaemia, infection, nail changes, anorexia, weight loss occurred at rates $\geq 10\%$ higher in patients who were 65 years of age or greater compared to younger patients.

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

Of the 174 and 251 patients who received the induction treatment with TAXOTERE 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.

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).

4.5 INTERACTION 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 cyclosporin, 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.

In case of combination with CYP3A4 inhibitors, the occurrence of TAXOTERE adverse reactions may increase, as a result of reduced metabolism. The concomitant use of TAXOTERE 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 TAXOTERE 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, α 1-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 TAXOTERE may alter the effects of other medicinal products.

4.6 PREGNANCY AND LACTATION

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 $0.9\text{mg}/\text{m}^2$, 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 $1.8\text{mg}/\text{m}^2$ or $1.2\text{mg}/\text{m}^2$ in rats or rabbits, respectively, but reduced foetal weight and delayed ossification were observed.

Offspring from rats receiving docetaxel $1.5\text{mg}/\text{m}^2/\text{day}$ 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. Contraceptive measures must be taken during and for at least three months after cessation of therapy with TAXOTERE.

Lactation

Radioactivity has been detected in milk following intravenous administration of radiolabelled docetaxel to lactating rats. Offspring from rats receiving docetaxel 1.5mg/m²/day IV during late gestation and lactation showed signs of delayed development. It is not known whether TAXOTERE is excreted in human milk. It is recommended to advise women not to breast-feed during treatment with TAXOTERE.

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. The amount of ethanol in TAXOTERE may impair the ability to drive or use machines.

4.8 UNDESIRABLE EFFECTS**Clinical Studies****Monotherapy****Breast and Non Small Cell Lung Cancer**

The adverse reactions considered to be possibly or probably related to starting the administration of TAXOTERE have been obtained from 75 patients who received a dose of 75mg/m² 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 100mg/m² 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 TAXOTERE for the treatment of breast, non small cell lung or ovarian carcinoma.

The following table lists the adverse reaction data:

Summary of adverse events in patients receiving TAXOTERE at 75 and 100mg/m² as a single agent

| | Normal LFTs* at Baseline | | Elevated LFTs* at Baseline |
|---------------------------------------|---------------------------|----------------------------|----------------------------|
| | 75mg/m ² | 100mg/m ² | 100mg/m ² |
| TAXOTERE dosage | 75mg/m² | 100mg/m² | 100mg/m² |
| Number of patients | n=75 | n=2045 | n=61 |
| | % | % | % |
| <i>Haematological Toxicity</i> | | | |

| TAXOTERE dosage | Normal LFTs* at Baseline | | Elevated LFTs* at Baseline |
|--|----------------------------|--------------------------------------|--------------------------------------|
| | 75mg/m ² | 100mg/m ² | 100mg/m ² |
| Number of patients | n=75 % | n=2045 % | n=61 % |
| <i>Neutropenia</i> ANC ⁻ <2.0 cells x 10 ⁹ /L ANC ⁻ <0.5 cells x 10 ⁹ /L | - 73.0 | 95.5 75.4 | 96.4 87.5 |
| <i>Febrile neutropenia</i> (fever/ANC ⁻ <0.5 x 10 ⁹ /L): by patient by cycle (fever/ANC ⁻ <1 x 10 ⁹ /L): by patient by cycle | - - 5.0 1.5 | 11.0 2.6* - - | 26.2 8.7 - - |
| <i>Thrombocytopenia</i> <100 cells x 10 ⁹ /L | 6.7 | 8.0 | 24.6 |
| <i>Anaemia</i> <110 g/L <80 g/L | 86.7 9.0 | 90.4 8.8 | 91.8 31.1 |
| Non-Haematological Toxicity | | | |
| <i>Body as a whole:</i> | | | |
| <i>Fluid retention</i> <i>Regardless of premedication:</i> All Severe 3 day <i>premedication:</i> All Severe | 61.0 9.3 - - | 47.0 6.9 [n=92] 64.1 6.5 | 39.3 8.2 [n=3] 66.7 33.3 |
| <i>Infections:</i> overall severe | 20.0 1.3 | 21.6* 6.1* | 32.8 16.4 |
| Asthenia All Severe Myalgia Arthralgia | 56.0 5.0 10.7 0.0 | 61.8 12.8 18.9 9.2 | 52.5 24.6 16.4 6.6 |

| TAXOTERE dosage | Normal LFTs* at Baseline | | Elevated LFTs* at Baseline |
|---|--------------------------|---------------------------|----------------------------|
| | 75mg/m ² | 100mg/m ² | 100mg/m ² |
| Number of patients | n=75 % | n=2045 % | n=61 % |
| <i>Neurological</i> | | | |
| <i>Neurosensory:</i> | | | |
| All | 37.0 | 49.3 | 34.4 |
| Severe | 1.3 | 4.3 | 0.0 |
| <i>Neuromotor</i> | | | |
| All | 4.0 | 13.8 | 6.6 |
| Severe | 0.0 | 3.6 | 1.6 |
| <i>Cutaneous</i> | | | |
| Skin: | | | |
| All | 45.3 | 47.6 | 54.1 |
| Severe | 1.3 | 4.8 | 9.8 |
| Nail disorders | 50.0 | 30.6 | 23.0 |
| Alopecia | 92.0 | 75.8 | 62.3 |
| <i>Gastrointestinal</i> | | | |
| 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 | - | - |
| <i>Infusion site reactions</i> consisting of hyperpigmentation, inflammation, redness or dryness of skin, phlebitis or extravasation and swelling of the vein | 5.6 | 4.4 | 3.3 |

* Normal liver function tests (LFTs): transaminase ≤ 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

Thirty-five toxic deaths (1.7%) were reported in the 2045 patients with normal baseline liver function tests treated with TAXOTERE as monotherapy at the initially planned dose of 100mg/m². 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**). Severe reactions resolved after discontinuing the infusion and appropriate therapy.

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 reaction, 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 $<0.5 \times 10^9/L$, 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.

Neurologic

Mild to moderate neuro-sensory signs and/or symptoms occurred in 50% of the patients. Severe neurosensory symptoms (paresthesia, dysesthesia, pain including burning) were observed in 4.1% of metastatic breast cancer patients, and resulted in treatment discontinuation in 2%. Neuro-motor events (13.8% with 4% severe) 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 $100\text{mg}/\text{m}^2$ 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 ($\geq 5\%$) reported in the phase III clinical trial for TAXOTERE 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.

Treatment-related adverse reactions reported in ≥5% of patients treated with TAXOTERE in combination with capecitabine

| Body system Adverse reaction | Capecitabine 1250mg/m ² twice daily with TAXOTERE 75mg/m ² /3 weeks (n=251) | | Docetaxel 100mg/m ² /3 weeks (n=255) | |
|---------------------------------|---|----------------|---|----------------|
| | All Grades % | Grade 3/4 % | All Grades % | Grade 3/4 % |
| 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 |
| Onycholysis | 5 | 1 | 5 | 1 |
| General | | | | |
| Asthenia | 23 | 3 | 22 | 5 |
| Pyrexia | 21 | 1 | 29 | <1 |
| Fatigue | 21 | 4 | 25 | 5 |
| Weakness | 13 | 1 | 9 | 2 |
| Pain in limb | 9 | <1 | 8 | <1 |
| Lethargy | 6 | – | 5 | 1 |
| Pain | 6 | – | 2 | – |
| Neurologic | | | | |
| Taste disturbance | 15 | <1 | 14 | <1 |
| Paresthesia | 11 | <1 | 15 | 1 |
| Dizziness | 9 | – | 6 | <1 |
| Headache | 7 | <1 | 8 | 1 |
| Peripheral neuropathy | 5 | – | 10 | 1 |
| 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 | – |

| Body system Adverse reaction | Capecitabine 1250mg/m ² twice daily with TAXOTERE 75mg/m ² /3 weeks (n=251) | | Docetaxel 100mg/m ² /3 weeks (n=255) | |
|--|---|----------------|---|----------------|
| | All Grades % | Grade 3/4 % | All Grades % | Grade 3/4 % |
| 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 |
| Arthralgia | 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 |
| Increase 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 were:

| Adverse Event | capecitabine with docetaxel (n=251) |
|--------------------------|--|
| Laboratory Abnormalities | Grade 3/4 % |
| Neutropenia | 63 |
| 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.

Adjuvant Treatment of Breast Cancer**Combination with Doxorubicin and Cyclophosphamide**

The following table presents clinically important treatment-emergent adverse events (TEAEs) observed in 744 patients, who were treated with TAXOTERE 75mg/m² every 3 weeks in combination with doxorubicin and cyclophosphamide and 736 patients, treated with the comparator study drugs.

Clinically important treatment emergent adverse events (TEAEs) considered related to study treatment in patients receiving TAXOTERE in combination with doxorubicin and cyclophosphamide

| | TAXOTERE 75mg/m² + Doxorubicin 50mg/m² + Cyclophosphamide 500mg/m² n=744 | | Fluorouracil 500mg/m² + Doxorubicin 50mg/m² + Cyclophosphamide 500mg/m² n=736 | |
|--------------------------------------|--|---------------------|---|---------------------|
| Body System Adverse Event | Any (%) | Grade 3/4 (%) | Any((%) | Grade 3/4 (%) |
| <i>CUTANEOUS</i> | | | | |
| 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 |
| <i>HAEMATOLOGIC</i> | | | | |
| Anaemia | 92.1 | 4.3 | 71.7 | 1.6 |
| Neutropenia | 71.8 | 65.5 | 82.0 | 49.3 |
| Thrombocytopenia | 39.5 | 2.0 | 27.7 | 1.2 |
| Febrile neutropenia | 24.7 | N/A | 2.5 | N/A |
| Neutropenic infection | 17.3 | N/A | 6.3 | N/A |
| <i>GASTROINTESTINAL</i> | | | | |
| 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 | 24.5 | 0.4 | 21.5 | 1.2 |
| Abdominal pain | 7.3 | 0.5 | 3.3 | 0.0 |
| <i>GENERAL</i> | | | | |
| Asthenia | 79.2 | 11.0 | 69.4 | 5.2 |
| Fever in absence of infection | 43.1 | 1.2 | 13.2 | 0.0 |
| Infection* | 29.2 | 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 |

| | TAXOTERE 75mg/m² + Doxorubicin 50mg/m² + Cyclophosphamide 500mg/m² n=744 | | Fluorouracil 500mg/m² + Doxorubicin 50mg/m² + Cyclophosphamide 500mg/m² n=736 | |
|--------------------------------------|--|---------------------|---|---------------------|
| Body System Adverse Event | Any (%) | Grade 3/4 (%) | Any((%) | Grade 3/4 (%) |
| <i>GYNAECOLOGIC</i> | | | | |
| Amenorrhoea | 57.6 | N/A | 48.1 | N/A |
| <i>NEUROLOGIC</i> | | | | |
| 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 |
| <i>MUSCULOSKELETAL</i> | | | | |
| Myalgia | 22.8 | 0.8 | 8.0 | 0.0 |
| Arthralgia | 15.1 | 0.4 | 5.7 | 0.3 |
| <i>CARDIOVASCULAR</i> | | | | |
| CHF | | | | |
| Vasodilatation/hot flush | 0.0 | 1.6 | 0.0 | 0.5 |
| Cardiac dysrhythmias** | 21.4 | 0.9 | 15.9 | 0.4 |
| Hypotension | 3.9 | 0.3 | 2.9 | 0.3 |
| Phlebitis | 1.5 | 0.0 | 0.5 | 0.0 |
| | 0.9 | 0.0 | 0.4 | 0.0 |
| <i>METABOLIC</i> | | | | |
| Anorexia | | | | |
| Weight gain or loss | 19.9 | 2.2 | 16.4 | 1.2 |
| | 15.2 | 0.3 | 9.2 | 0.0 |
| <i>EYE</i> | | | | |
| Lacrimation disorder | | | | |
| Conjunctivitis | 10.1 | 0.1 | 6.4 | 0.0 |
| | 4.6 | 0.3 | 6.0 | 0.1 |
| <i>RESPIRATORY</i> | | | | |
| Cough | | | | |
| | 3.1 | 0.0 | 2.2 | 0.1 |

N/A

not applicable

*

there was no septic death in either treatment arms

**

one patient died due to heart failure in TAC arm

Of the 744 patients treated with TAC, 33.1% experienced severe TEAEs. Dose reductions due to haematologic 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 43.1% of patients and infection was seen in 29.2% of patients. There were no septic deaths during the study period.

Gastrointestinal Events

In addition to gastrointestinal events reflected in the above table, 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 TAXOTERE, doxorubicin and cyclophosphamide and in one of 736 (0.1%) patients who receive fluorouracil, doxorubicin and cyclophosphamide. One TAC patient died due to AML during the follow up period.

Cardiovascular Events

The following treatment emergent cardiovascular events were reported during the study period: dysrhythmias, all grades (6.2%), hypotension, all grades (1.9%) and CHF (3.5%). Twenty-six patients in the TAC group developed CHF during the study period, with most cases reported in the follow-up period. CHF lead to death in 2 TAC patients and in 4 FAC patients. The risk of CHF is higher in the TAC group in the first year.

Other Persistent Reactions

The most common adverse events persisting into the follow-up period in TAC patients were alopecia (92.3%), asthenia (31.7%), and amenorrhoea (27.2%). Among the adverse events that persisted into the follow-up period in >1% of patients, the majority of events resolved; however, amenorrhoea (59.9%), and lymphoedema (54.5%) remained ongoing in TAC patients.

Combination with Doxorubicin, Cyclophosphamide and Trastuzumab and with Carboplatin and Trastuzumab (HER2+)

Adverse Events (AEs) Related to Study Treatment, Occurring at Any Time During the Study: Safety population (incidence of $\geq 5\%$ for non-cardiac AEs; incidence of $\geq 1\%$ for cardiac AEs)

| Adverse Event (NCI-CTC term) | AC-T n=1050 | | AC-TH n=1068 | | TCH n=1056 | |
|------------------------------|------------------|--------------------|------------------|-----------------------|------------------|-----------------------|
| | Overall n (%) | Grade 3/4 n (%) | Overall n (%) | Grade 3/4 n (%) | Overall n (%) | Grade 3/4 n (%) |
| Alopecia | 1029 (98.0) | 0 | 1047 (98.0) | 0 | 1012 (95.8) | 0 |
| 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) |

| | AC-T n=1050 | | AC-TH n=1068 | | TCH n=1056 | |
|-----------------------------------|------------------------|------------|-------------------------|------------|-----------------------|------------|
| 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) |
| Dyspnea | 156 (14.9) | 8 (0.8) | 166 (15.5) | 16 (1.5) | 157 (14.9) | 18 (1.7) |
| Weight gain | 114 (10.9) | 3 (0.3) | 159 (14.9) | 3 (0.3) | 154 (14.6) | 2 (0.2) |
| Infection without neutropenia | 105 (10.0) | 17 (1.6) | 135 (12.6) | 20 (1.9) | 98 (9.3) | 16 (1.5) |
| Abdominal pain or cramping | 108 (10.3) | 3 (0.3) | 132 (12.4) | 4 (0.4) | 141 (13.4) | 5 (0.5) |
| Insomnia | 106 (10.1) | 0 | 119 (11.1) | 1 (0.1) | 93 (8.8) | 0 |
| Febrile neutropenia | 95 (9.0) | 95 (9.0) | 116 (10.9) | 116 (10.9) | 103 (9.8) | 103 (9.8) |
| Fever (without neutropenia) | 95 (9.0) | 3 (0.3) | 116 (10.9) | 4 (0.4) | 70 (6.6) | 3 (0.3) |
| Allergic | 75 (7.1) | 12 (1.1) | 105 (9.8) | 15 (1.4) | 139 (13.2) | 26 (2.5) |

| | AC-T n=1050 | | AC-TH n=1068 | | TCH n=1056 | |
|--------------------------------------|----------------|----------|-----------------|----------|---------------|----------|
| reaction/hypersensitivity | | | | | | |
| 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 |
| 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 TAXOTERE

AC-TH = doxorubicin and cyclophosphamide, followed by TAXOTERE in combination with trastuzumab. TCH = TAXOTERE 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 **Clinical Trials** section). 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).

Prostate Cancer

Combination with Prednisone or Prednisolone

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

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 TAXOTERE 75mg/m² q3w and mitozantrone q3w in combination with prednisone (or prednisolone).

Clinically important treatment emergent adverse events related to study medication

| | TAXOTERE 75mg/m ² every 3 weeks (n=332) % | | Mitozantrone 12mg/m ² every 3 weeks (n=335) % | |
|-------------------------|--|------|--|------|
| | Grade 3/4 | Any | Grade 3/4 | Any |
| <i>Cutaneous</i> | | | | |
| 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 |
| <i>Haematologic</i> | | | | |
| 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 |
| <i>General</i> | | | | |
| 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 |
| <i>Gastrointestinal</i> | | | | |
| 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 |
| <i>Neurologic</i> | | | | |
| 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 |
| <i>Respiratory</i> | | | | |
| Dyspnea | 0.6 | 4.5 | 0.3 | 3.3 |
| Cough | 0.0 | 1.2 | 0.0 | 0.9 |
| <i>Eye</i> | | | | |

| | TAXOTERE 75mg/m ² every 3 weeks (n=332) % | | Mitozantrone 12mg/m ² every 3 weeks (n=335) % | |
|---|--|-----|--|------|
| | Grade 3/4 | Any | Grade 3/4 | Any |
| Tearing | 0.6 | 9.3 | 0.0 | 1.5 |
| <i>Musculoskeletal</i> | | | | |
| Myalgia | 0.3 | 6.9 | 0.0 | 3.3 |
| Arthralgia | 0.3 | 3.0 | 0.0 | 0.6 |
| <i>Cardiovascular</i> | | | | |
| Abnormal cardiac left ventricular function | 0.3 | 3.9 | 0.9 | 19.1 |

* NA: 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 TAXOTERE 75mg/m² in combination with cisplatin and fluorouracil.

Clinically Important Treatment-Related Adverse Events in Patients with SCCHN Receiving TAXOTERE in Combination with Cisplatin and Fluorouracil

| Adverse Event | TAX323: TAXOTERE 75mg/m ² + cisplatin 75mg/m ² + fluorouracil 750mg/m ² (n=174) | | TAX 324: TAXOTERE 75mg/m ² + cisplatin 100mg/m ² + fluorouracil 1000mg/m ² (n=251) | |
|---|--|----------------|--|----------------|
| | Any % | Grade 3/4 % | Any % | Grade 3/4 % |
| <i>Blood and lymphatic system</i> | | | | |
| 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 |
| <i>Skin and subcutaneous tissue disorders</i> | | | | |
| 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 |

| Adverse Event | TAX323: TAXOTERE 75mg/m ² + cisplatin 75mg/m ² + fluorouracil 750mg/m ² (n=174) | | TAX 324: TAXOTERE 75mg/m ² + cisplatin 100mg/m ² + fluorouracil 1000mg/m ² (n=251) | |
|--|--|----------------|--|----------------|
| | Any % | Grade 3/4 % | Any % | Grade 3/4 % |
| Oedema only | 12.6 | 0.0 | 12.0 | 1.2 |
| Weight gain only | 5.7 | 0.0 | 0.4 | 0.0 |
| <i>Gastrointestinal disorders</i> | | | | |
| Nausea | 43.7 | 0.6 | 75.7 | 13.9 |
| Stomatitis | 42.0 | 4.0 | 64.5 | 20.7 |
| 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/odyn ophagia | 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 |
| <i>Nervous system disorders</i> | | | | |
| Neurosensory | 16.7 | 0.6 | 11.6 | 1.2 |
| Neuromotor | - | - | 7.2 | 0.4 |
| Dizziness | 1.1 | | 9.6 | 2.0 |
| <i>Cardiac disorders</i> | | | | |
| Myocardial Ischemia | 1.7 | 1.7 | 0.8 | 0.8 |
| Cardiac dysrhythmia | 0.6 | 0.6 | 3.2 | 0.2 |
| <i>Vascular disorders</i> | | | | |
| Venous | 1.1 | 0.6 | 0.8 | 0.4 |
| <i>Metabolism and nutrition disorders</i> | | | | |
| Anorexia | 15.5 | 0.6 | 37.8 | 12.0 |
| Weight loss | 9.8 | 0 | 11.2 | 0.0 |
| <i>Eye disorders</i> | | | | |
| Tearing | 1.7 | 0 | 1.6 | 0.0 |
| Conjunctivitis | 1.1 | 0 | 0.8 | 0.0 |
| <i>Ear and labyrinth disorders</i> | | | | |
| Altered hearing | 5.7 | 0 | 11.2 | 1.2 |
| <i>Musculoskeletal, connective tissue and bone disorders</i> | | | | |
| Myalgia | 6.3 | 0.6 | 5.2 | 0.4 |
| <i>General disorders and administration site conditions</i> | | | | |
| 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 TAXOTERE. 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 $\geq 1-10\%$, 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 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 erythematosus and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes have been reported. Multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects. Cases of permanent alopecia have been reported.

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

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, colitis including ischemic colitis, gastrointestinal haemorrhage, dehydration as a consequence of gastrointestinal events including enterocolitis and gastrointestinal perforation.

Very rare: duodenal ulcer.

Neurologic

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

Cardiovascular

Common: hypertension, hypotension.

Uncommon: cardiac arrhythmia, congestive heart failure.

Rare: atrial fibrillation, syncope, tachycardia, myocardial infarction, deep vein thrombosis.

Very rare: ECG abnormalities, thrombophlebitis, pulmonary embolism.

Ventricular arrhythmia including ventricular tachycardia, sometimes fatal, has been reported in patients treated with docetaxel in combination regimens including doxorubicin, fluorouracil and/or cyclophosphamide.

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.

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.

General disorders and administration site conditions

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

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.

Reporting of 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 using the following website link: <https://nzphvc.otago.ac.nz/reporting>

4.9 OVERDOSE

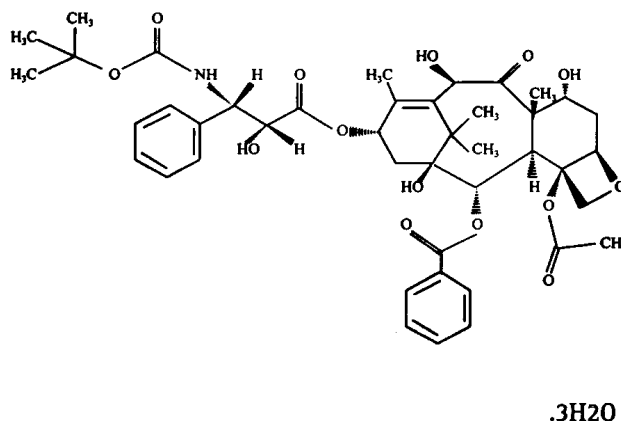
In case of overdosage, the patient should be kept in a specialised unit and vital functions closely monitored. There is no known antidote for TAXOTERE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

There were two reports of overdose. One patient received 150mg/m² and the other received 200mg/m² of TAXOTERE as a one hour infusion. They both recovered after experiencing severe neutropenia, mild asthenia, cutaneous reactions and mild paraesthesia.

Contact the Poisons Information Centre (0800 POISON or 0800 764 766) for advice on management of overdosage.

5 PHARMACOLOGICAL PROPERTIES

Chemical Structure



CAS Number

148408-66-6

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

Docetaxel is a white to almost white powder with the empirical formula C₄₃H₅₃NO₁₄.3H₂O and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

5.1 PHARMACODYNAMIC PROPERTIES

Class

TAXOTERE 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.

Site and Mode of Action

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

5.2 PHARMACOKINETIC PROPERTIES

Distribution

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5-115mg/m² 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

100mg/m² dose given as a one-hour infusion a mean peak plasma level of 3.7µg/mL was obtained with a corresponding AUC of 4.6h.µg/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m² and 113 L, respectively.

Metabolism and Excretion

A study of ¹⁴C-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.

A population pharmacokinetic analysis has been performed with TAXOTERE 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**). 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.

5.3 PRECLINICAL SAFETY DATA

TAXOTERE 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, TAXOTERE was found to be active on some, but not all, cell lines overexpressing the *p*-glycoprotein which is encoded by the multidrug resistance gene. *In vivo*, TAXOTERE 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.

Carcinogenicity

TAXOTERE 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.

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

Studies in mice have shown that IV doses of 144mg/m² or 30mg/m²/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 120mg/m² are associated with testicular atrophy, germ cell atrophy, Leydig cell hyperplasia and mineralisation. The rodent studies suggest that TAXOTERE may impair fertility. Studies in rats have also shown that IV doses of 0.9mg/m²/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 1.8mg/m²/day, females 1.35mg/m²/day) are additionally associated with increased time to mating, increased number of dams with total resorption, and reduced male foetal body weight.

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, TAXOTERE was administered at a 75mg/m² dose in 55 previously untreated patients and 100mg/m² in 117 previously untreated and 111 previously treated patients. In these trials, TAXOTERE was administered as a one-hour infusion every 3 weeks.

Patients Treated at 75mg/m²

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 100mg/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 100mg/m² 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 100mg/m² 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; 75mg/m² 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; 12mg/m² every 6 weeks and 6mg/m² 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 TAXOTERE 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 either TAXOTERE 100mg/m² as a one hour infusion or paclitaxel 175 mg/m² as a 3 hour infusion. Both regimes were administered every 3 weeks. Efficacy results are described in the following table.

Efficacy of TAXOTERE versus paclitaxel in the treatment of advanced breast cancer (Intent-to-Treat Analysis, unless specified)

| Endpoint | TAXOTERE 100mg/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 TAXOTERE were neutropenia, febrile neutropenia, gastrointestinal disorders, neurologic disorders, asthenia and fluid retention.

More grade 3/4 events were observed from TAXOTERE (55.4%) compared to paclitaxel (23.0%). No unexpected toxicities were reported for TAXOTERE.

Combination with Capecitabine

TAXOTERE 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 (1250mg/m² twice daily for 2 weeks followed by a 1 week rest period) in combination with docetaxel (75mg/m² as a 1 hour intravenous infusion every 3 weeks). 256 patients received docetaxel 100mg/m² alone.

TAXOTERE 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.

Breast cancer combination treatment efficacy results¹

| 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

Adjuvant Treatment of Breast Cancer

Combination with Doxorubicin and Cyclophosphamide

Data from a multicentre open label randomized trial support the use of TAXOTERE for the adjuvant treatment of patients with node-positive breast cancer and KPS \geq 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 TAXOTERE 75mg/m² administered 1 hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² (TAC arm), or doxorubicin 50mg/m² followed by fluorouracil 500mg/m² and cyclophosphamide 500mg/m² (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. TAXOTERE 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 TAXOTERE arm who continued to experience these reactions remained on G-CSF and had their dose reduced to 60mg/m². Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500mg 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 20mg 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), TAXOTERE 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:

Analysis of TAC-treated patient subsets

| Patient subset | Number of patients | Disease Free Survival | | | Overall Survival | | |
|--------------------------------|--------------------|-----------------------|-----------|--------|------------------|-----------|--------|
| | | Hazard ratio* | 95% CI | P= | Hazard ratio* | 95% CI | P= |
| No of positive nodes | | | | | | | |
| Overall | 745 | 0.72 | 0.59-0.88 | 0.001 | 0.70 | 0.53-0.91 | 0.008 |
| 1-3 | 467 | 0.61 | 0.46-0.82 | 0.0009 | 0.45 | 0.29-0.70 | 0.0002 |
| 4+ | 278 | 0.83 | 0.63-1.08 | 0.17 | 0.94 | 0.66-1.33 | 0.72 |
| 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 TAXOTERE 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/m² IV in combination with cyclophosphamide 600 mg/m² IV every 3 weeks for 4 cycles, followed by TAXOTERE 100 mg/m² as a 1-hour IV infusion every 3 weeks for 4 cycles;

- AC-TH: Doxorubicin 60 mg/m² IV in combination with cyclophosphamide 600 mg/m² 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 TAXOTERE 100

mg/m² 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 TAXOTERE. 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. TAXOTERE 75 mg/m² 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 TAXOTERE 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 TAXOTERE 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 relative reduction in the risk of relapse was 39 % (p < 0.0001) and 33% (p = 0.0003) for the AC-TH and TCH arms, respectively, compared with the AC-T arm. The relative reduction in the risk of death was 42% (p = 0.0024) and 34% (p = 0.0182) for the AC-TH and TCH arms, respectively, compared with the AC-T arm. 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:

Doxorubicin and cyclophosphamide followed by TAXOTERE in combination with trastuzumab, or TAXOTERE in combination with trastuzumab, and carboplatin (Intent to Treat Population)

| | Disease Free Survival (DFS) | | | Overall Survival (OS) | | |
|---------------------------|-----------------------------|-----------------|-----------------|-----------------------|-----------------|-----------------|
| | AC-T n=1073 | AC-TH n=1074 | TCH n=1075 | AC-T n=1073 | AC-TH n=1074 | TCH n=1075 |
| Stratified analysis | | | | | | |
| Hazard ratio ^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 TAXOTERE; AC-TH=doxorubicin plus cyclophosphamide, followed by TAXOTERE in combination with trastuzumab; TCH=TAXOTERE 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.

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

| | High risk node-negative patients | | | Node-positive patients | | |
|--|----------------------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|
| | AC-T n = 309 | AC-TH n = 306 | TCH n = 307 | AC-T n = 764 | AC-TH n = 768 | TCH n = 768 |
| Stratified analysis | | | | | | |
| Hazard ratio ^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% (84.1-91.9%) | 94.8% (91.9-97.8%) | 93.0% (89.9-96.2%) | 78.1% (74.9-81.3%) | 83.6% (80.7-86.5%) | 82.6% (79.6-85.6%) |
| Absolute benefit ^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 TAXOTERE; AC-TH=doxorubicin plus cyclophosphamide, followed by TAXOTERE in combination with trastuzumab; TCH=TAXOTERE 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.

Non Small Cell Lung Cancer

Patients Treated at 75mg/m²

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, TAXOTERE was administered at a 75mg/m² dose given as a one-hour infusion every 3 weeks. The response rate was 10%.

Patients Treated at 100mg/m²

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, TAXOTERE was administered at a 100mg/m² dose given as a one-hour infusion every 3 weeks.

The 100mg/m² 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.

Prostate Cancer

The safety and efficacy of TAXOTERE 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:

- TAXOTERE 75mg/m² every 3 weeks for 10 cycles.
- TAXOTERE 30mg/m² administered weekly for the first 5 weeks in a 6 week cycle for 5 cycles.
- Mitozantrone 12mg/m² every 3 weeks for 10 cycles.

All 3 regimens were administered in combination with prednisone or prednisolone 5mg 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 TAXOTERE 3 weekly arm versus the control arm are summarised in the following table:

Efficacy of TAXOTERE in the treatment of patients with androgen independent (hormone refractory) prostate cancer (intent-to-treat analysis)

| Endpoint | TAXOTERE 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 | - |

| Endpoint | TAXOTERE Every 3 weeks | Mitozantrone Every 3 weeks |
|--------------------------|---------------------------|-------------------------------|
| 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 TAXOTERE 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 TAXOTERE arm received TAXOTERE (T) 75mg/m² followed by cisplatin (P) 75mg/m² on Day 1, followed by fluorouracil (F) 750mg/m² per day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Premedication for TAXOTERE included corticosteroids and antibiotics. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin 100mg/m² on Day 1, followed by fluorouracil 1000mg/m² (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.

Efficacy of TAXOTERE in the induction treatment of patients with locally advanced inoperable SCCHN (intent-to-treat analysis)

| Endpoint | TAXOTERE + 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) ***p-value | 72.3 (65.1 – 78.8) | 58.6 (51.0 – 65.8) |
| | 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 TAXOTERE + 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 TAXOTERE in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomised, multicentre open-label, phase III trial (TAX324). 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 TAXOTERE arm received TAXOTERE (T) 75 mg/m² by IV infusion on day 1, followed by cisplatin (P) 100 mg/m² administered as a 30 minute to three hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. Premedication for TAXOTERE included corticosteroids and antibiotics. 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/m² administered as a 30 minute to three hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients 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 TAXOTERE-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 the table below.

Efficacy of TAXOTERE in the induction treatment followed by chemoradiotherapy for patients with locally advanced SCCHN (Intent-to-treat analysis)

| Endpoint | TAXOTERE + 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 chemotherapy (%) (95% CI) | 71.8 (65.8 – 77.2) | 64.2 (57.9 – 70.2) |
| ***p-value | 0.070 | |
| Best overall response (CR + PR) to study treatment [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 TAXOTERE + 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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polysorbate 80

Ethanol

Water for Injection

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Do not mix the reconstituted two vial formulation (injection concentrate and diluent) with the single vial formulation, either before or after preparation of the infusion solution.

6.3 SHELF LIFE

TAXOTERE 20mg: store for 24 months.

TAXOTERE 80mg: store for 36 months.

Storage of the TAXOTERE Premix Solution (10mg docetaxel/mL)

The premix solution should be used immediately after preparation. The chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either in the refrigerator or at room temperature. However, if storage is necessary, store the premix in the refrigerator to reduce microbiological hazards.

Storage of the TAXOTERE solution for infusion

To reduce microbiological hazards and the risk of crystallisation of docetaxel from diluted solutions, it is recommended that reconstitution and further dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. If storage of the solution for infusion is necessary, store at room temperature (below 25°C) and administer within 4 hours (including the 1 hour infusion). Any residue after infusion should be discarded. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TAXOTERE 20mg: store below 25°C and protect from light.

TAXOTERE 80mg: store below 25°C and protect from light.

For storage conditions after reconstitution see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

TAXOTERE concentrate for infusion to be diluted is supplied in single-dose vials as a sterile pyrogen-free non-aqueous clear yellow to brown yellow viscous solution with the accompanying sterile solvent (13% ethanol in water for injections). The following strengths are available:

TAXOTERE 20mg*

Each blister carton contains one single-dose TAXOTERE (docetaxel) parenteral preparation to be diluted equivalent to 20mg docetaxel (anhydrous) in 0.5mL polysorbate 80 (Fill: 24.4mg/0.61mL) and one single-dose TAXOTERE Solvent vial containing 1.98mL 13% ethanol in water for injections. Each vial of solvent contains 252 mg of ethanol 95% v/v.

TAXOTERE 80mg*

Each blister carton contains one single-dose TAXOTERE (docetaxel) parenteral preparation to be diluted equivalent to 80mg docetaxel (anhydrous) in 2mL polysorbate 80 (Fill: 94.4mg/2.36mL) and one single-dose TAXOTERE Solvent vial containing 7.33mL 13% ethanol in water for injections. Each vial of solvent contains 932 mg of ethanol 95% v/v.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Recommendations for Safe Handling

TAXOTERE is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TAXOTERE solutions. The use of gloves is recommended.

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

Preparation for the Intravenous Administration

Note: Do not mix the reconstituted two vial formulation (injection concentrate and diluent) with the single vial formulation, either before or after preparation of the infusion solution.

TAXOTERE 20mg Concentrate and Solvent Vials

TAXOTERE 20mg concentrate vial contains 0.5 mL of a 40mg/mL solution of docetaxel in polysorbate 80 (fill volume: 24.4mg/0.61 mL). This fill volume has been established during the development of TAXOTERE to compensate for liquid loss during preparation of the premix solution due to foaming, adhesion to the walls of the vial, and the “dead volume”. This overfill ensures that after dilution with the entire contents of the accompanying TAXOTERE Solvent vial, there is an initial diluted solution of 2mL containing 10mg/mL docetaxel which correspond to the labelled amount of 20mg per vial.

Solvent vial contains 1.5 mL of a 13% w/w solution of ethanol in water for injections (fill volume: 1.98mL). The addition of the entire contents of the solvent vial to the content of the TAXOTERE 20mg concentrate vial ensures a premix concentration of 10mg/mL docetaxel.

TAXOTERE 80mg Concentrate and Solvent vials

TAXOTERE 80mg concentrate vial contains 2 mL of a 40mg/mL solution of docetaxel in polysorbate 80 (fill volume: 94.4mg/2.36 mL). This fill volume has been established during the development of TAXOTERE to compensate for liquid loss during preparation of the premix solution due to foaming, adhesion to the walls of the vial, and the “dead volume”. This overfill ensures that after dilution with the entire contents of the accompanying TAXOTERE Solvent vial, there is an initial diluted solution of 8mL containing 10mg/mL docetaxel which correspond to the labelled amount of 80mg per vial.

Solvent vial contains 6 mL of a 13% w/w solution of ethanol in water for injections (fill volume: 7.33mL). The addition of the entire contents of the solvent vial to the content of the TAXOTERE 80mg concentrate vial ensures a premix concentration of 10mg/mL docetaxel.

a) Preparation of the TAXOTERE Premix Solution (10mg docetaxel/mL)

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the TAXOTERE Solvent vial by partially inverting the vial. Inject the entire contents of the syringe into the corresponding TAXOTERE vial. Remove the syringe and needle and mix the vial by repeated inversions for at least 45 seconds. Do not shake. Allow the TAXOTERE premix solution to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation.

The premix solution contains 10mg/mL docetaxel. As with all parenteral products, TAXOTERE premix solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

b) Preparation of the Infusion Solution

More than one premix vial may be necessary to obtain the required dose for the patients. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding premix volume containing 10mg/mL docetaxel from the appropriate number of premix vials using a graduated syringe fitted with a 21 gauge needle. For example, a dose of 140mg docetaxel would require 14mL docetaxel premix solution.

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

As with all parenteral products, TAXOTERE solution for infusion should be visually inspected prior to use, and solutions containing a precipitate should be discarded.

TAXOTERE solution for infusion should be aseptically administered intravenously as a one-hour infusion under room temperature and normal lighting conditions.

c) Disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8,
56 Cawley Street
Ellerslie, Auckland
NEW ZEALAND

Freecall No: 0800 283 684

9 DATE OF FIRST APPROVAL

7 October 2010

10 DATE OF REVISION OF THE TEXT

30 November 2017

*not marketed in New Zealand

SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|------------------------|---|
| 1 | Product name format change |
| 4.2 | Spelling correction of neutropenia, neutropenic and thrombocytopenia |
| 4.4 | Spelling correction of neutropenia, neutropenic and thrombocytopenia |
| 4.4 | Addition of Gastrointestinal reactions |
| 4.4 | Addition to Hypersensitivity reactions |
| 4.8 | Spelling correction of neutropenia, neutropenic thrombocytopenia, leukopenia and hyperbilirubinemia |
| 4.8 | Addition to Hypersensitivity section in Post Marketing Reactions |
| 4.8 | Addition to Gastrointestinal section in Post Marketing Reactions |
| 4.8 | Addition of General disorders and administration site conditions |
| 4.8 | Headings updated: Blood and lymphatic disorders, Renal and urinary disorders |
| 4.9 | Spelling correction of neutropenia |
| 5.3 | Spelling correction of neutropenia and neutropenic |
| 10 | Updated to 30 November 2017 |