Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Docetaxel Teva Generics 80 mg Powder and Solvent for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial of 80 mg powder contains 80 mg of docetaxel anhydrous. The reconstituted solution contains 5 mg/ml of docetaxel (anhydrous).

Each single-dose vial of solvent contains 13.4 ml water for injection.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.
The powder is a white, lyophilised powder or cake, free from extraneous particles.

The solvent is a colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Breast cancer

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

Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

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

Docetaxel in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

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

Prostate cancer

Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric Adenocarcinoma

Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

Head and neck cancer

Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

4.2 Posology and method of administration

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy (see section 6.6).

Recommended dose

For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used (see section 4.4). Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
For prostate cancer, given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see section 4.4).

Docetaxel is administered as a one-hour infusion every three weeks.

Breast cancer

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel is 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (see also Dose adjustments during treatment).
For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).

In combination with trastuzumab the recommended dose of docetaxel is 100 mg/m^2 every three weeks, with trastuzumab administered weekly. In the pivotal study the initial docetaxel infusion was started the day following the first dose of trastuzumab. The subsequent docetaxel doses were administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. For trastuzumab dosage and administration, see traztuzumab summary of product characteristics.

In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m^2 every three weeks, combined with capecitabine at 1250 mg/m^2 twice daily (within 30 minutes after a meal) for 2 weeks followed by 1- week rest period. For capecitabine dose calculation according to body surface area, see capecitabine summary of product characteristics.

Non-small cell lung cancer

In chemotherapy naïve patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dosage is 75 mg/m² as a single agent.

Prostate cancer

The recommended dose of docetaxel is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously (see section 5.1).

Gastric adenocarcinoma

The recommended dose of docetaxel is 75 mg/m^2 as a 1 hour infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg /m^2 per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion.
Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of haematological toxicities (See also Dose adjustments during treatment).

Head and neck cancer

Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities. All patients on the docetaxel-containing arm of the innovator's studies TAX 323 and TAX 324, received prophylactic antibiotics.

- Induction chemotherapy followed by radiotherapy (TAX 323)
  For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)
  For the induction treatment of patients with locally advanced (technically unresectable, low probability of surgical cure, and aiming at organ preservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy.

For cisplatin and 5-fluorouracil dose modifications, see the corresponding summary of product characteristics.

Dose adjustments during treatment

General

Docetaxel should be administered when the neutrophil count is ≥1,500 cells/mm^3.
In patients who experienced either febrile neutropenia, neutrophil count <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², the treatment should be discontinued.

Adjuvant therapy for breast cancer

In the pivotal study in patients who received adjuvant therapy for breast cancer and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g., day 4 to 11) in all subsequent cycles. Patients who continued to experience this reaction should remain on G-CSF and have their docetaxel dose reduced to 60 mg/m².
However, in clinical practice neutropenia could occur earlier. Thus the use of G-CSF should be considered function of the neutropenic risk of the patient and current recommendations. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60 mg/m².

In combination with cisplatin

For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is <25,000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the docetaxel dose in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see the corresponding summary of product characteristics.

In combination with capecitabine

- For capecitabine dose modifications, see capecitabine summary of product characteristics.
- For patients developing the first appearance of a Grade 2 toxicity, which persists at the time of the next docetaxel/capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100% of the original dose.
- For patients developing the second appearance of a Grade 2 toxicity, or the first appearance of a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with docetaxel 55 mg/m².
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose.

For trastuzumab dose modifications, see trastuzumab summary of product characteristics.

In combination with cisplatin and 5-fluorouracil

If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist. (See section 4.4).

Recommended dose modifications for toxicities in patients treated with docetaxel in combination with cisplatin and 5-fluorouracil (5-FU):

Toxicity	**Dosage adjustment**
Diarrhoea grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.
Diarrhoea grade 4	First episode: reduce docetaxel and 5-FU doses by 20%. Second episode: discontinue treatment.
Stomatitis/mucositis grade 3	First episode: reduce 5-FU dose by 20%. Second episode: stop 5-FU only, at all subsequent cycles. Third episode: reduce docetaxel dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%.

For cisplatin and 5-fluorouracil dosage adjustments, see the corresponding summary of product characteristics.

In the pivotal SCCHN studies patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg, day 6-15) in all subsequent cycles.

Special populations:

Patients with hepatic impairment

Based on pharmacokinetic data with docetaxel at 100 mg/m² as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2 (see sections 4.4 and 5.2). For those patients with serum bilirubin >ULN and/or ALT and AST >3.5 times the ULN associated with alkaline phosphatase >6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical study excluded patients with ALT and/or AST > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin > 1 x ULN; for these patients, no dose-reductions can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination

in the other indications.

Children and adolescents
The experience in children is limited.

Elderly
Based on a population pharmacokinetic analysis, there are no special instructions for use in the elderly. In combination with capecitabine, for patients 60 years of age or more, a starting dose reduction of capecitabine to 75% is recommended (see capecitabine summary of product characteristics).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Docetaxel must not be used in patients with baseline neutrophil count of <1,500 cells/mm^3.

Docetaxel must not be used in patients with severe liver impairment since there is no data available (see sections 4.2 and 4.4).

Contraindications for other medicinal products also apply, when combined with docetaxel.

4.4 Special warnings and precautions for use

For breast and non-small cell lung cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. For prostate cancer, the premedication is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see section 4.2).

Haematology
Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level ≥1,500 cells/mm^3 (see section 4.2).

In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended (see section 4.2).

In patients treated with docetaxel in combination with cisplatin and 5-fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G-CSF. Patients treated with TCF should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TCF should be closely monitored, (see sections 4.2 and 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 following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Cutaneous reactions

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation which lead to interruption or discontinuation of docetaxel treatment were reported (see section 4.2).

Fluid retention

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Patients with liver impairment

In patients treated with docetaxel at 100 mg/m^2 as single agent who have serum transaminase levels (ALT and/or AST) greater than 1.5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of docetaxel in those patients with elevated liver function test (LFTs) is 75 mg/m^2 and LFTs should be measured at baseline and before each cycle (see section 4.2).
For patients with serum bilirubin levels >ULN and/or ALT and AST >3.5 times the ULN concurrent with serum alkaline phosphatase levels >6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.
In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical study excluded patients with ALT and/or AST > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin> 1 x UNL; for these patients, no dose-reductions can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination in the other indications.

Patients with renal impairment

There are no data available in patients with severely impaired renal function treated with docetaxel.
Although renal accumulation has been described for other cyclodextrins, hydroxypropylbetadex is not associated with nephrotoxicity. Extra monitoring of renal function in renally impaired patients is therefore not considered necessary.

Nervous system

The development of severe peripheral neurotoxicity requires a reduction of dose (see section 4.2).

Cardiac toxicity

Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8).

When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment. Cardiac function should be further monitored during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction. For more details see Summary of Product Characteristics of trastuzumab.

Others

Contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy (see section 4.6).

Additional cautions for use in adjuvant treatment of breast cancer

Complicated neutropenia

For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G-CSF and dose reduction should be considered (see section 4.2).

Gastrointestinal reactions
Symptoms such as early abdominal pain and tenderness, fever, diarrhoea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.

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

Leukaemia
In the docetaxel, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow-up.

Patients with 4+ nodes
The benefit/risk ratio for TAC in patients with 4+ nodes was not defined fully at the interim analysis (see section 5.1).

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

Of the 333 patients treated with docetaxel every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the incidence of related nail changes occurred at a rate ≥ 10% higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, diarrhoea, anorexia, and peripheral oedema occurred at rates ≥ 10% higher in patients who were 75 years of age or greater versus less than 65 years.

Among the 300 (221 patients in the phase III part of the study and 79 patients in the phase II part) patients treated with docetaxel in combination with cisplatin and 5-fluorouracil in the gastric cancer study, 74 were 65 years of age or older and 4 patients were 75 years of age or older. The incidence of serious adverse events was higher in the elderly patients compared to younger patients.
The incidence of the following adverse events (all grades): lethargy, stomatitis, neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients.
Elderly patients treated with TCF should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P_{450}-3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

Docetaxel is highly protein bound (>95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicinal product has not been investigated formally, *in vitro* interactions with tightly protein-bound agents such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel. In addition, dexamethasone did not affect protein binding of docetaxel. Docetaxel did not influence the binding of digitoxin.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration. Limited data from a single uncontrolled study were suggestive of an interaction between docetaxel and carboplatin. When combined to docetaxel, the clearance of carboplatin was about 50% higher than values previously reported for carboplatin monotherapy.

Docetaxel pharmacokinetics in the presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolised by CYP3A4 and prednisone is known to induce CYP3A4.
No statistically significant effect of prednisone on the pharmacokinetics of docetaxel was observed.

Docetaxel should be administered with caution in patients concomitantly receiving potent CYP3A4 inhibitors (e.g.

protease inhibitors like ritonavir, azole antifungals like ketoconazole or itraconazole). A drug interaction study performed in patients receiving ketoconazole and docetaxel showed that the clearance of docetaxel was reduced by half by ketoconazole, probably because the metabolism of docetaxel involves CYP3A4 as a major (single) metabolic pathway. Reduced tolerance of docetaxel may occur, even at lower doses.

4.6 Fertility, pregnancy and lactation

There is no information on the use of docetaxel in pregnant women. Docetaxel has been shown to be both embryotoxic and foetotoxic in rabbits and rats, and to reduce fertility in rats. As with other cytotoxic medicinal products, docetaxel may cause foetal harm when administered to pregnant women. Therefore, docetaxel must not be used during pregnancy unless clearly indicated.

Women of childbearing potential/contraception:
Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

An effective method of contraception should be used during treatment. In non clinical studies, docetaxel has genotoxic effects and may alter male fertility (see section 5.3). Therefore, men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

Lactation:
Docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk.
Consequently, because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of docetaxel therapy.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions considered to be possibly or probably related to the administration of docetaxel have been obtained in:

- 1312 and 121 patients who received 100 mg/m² and 75 mg/m² of docetaxel as a single agent respectively.
- 258 patients who received docetaxel in combination with doxorubicin.
- 406 patients who received docetaxel in combination with cisplatin.
- 92 patients treated with docetaxel in combination with trastuzumab.
- 255 patients who received docetaxel in combination with capecitabine.
- 332 patients who received docetaxel in combination with prednisone or prednisolone (clinically important treatment related adverse events are presented).
- 744 patients who received docetaxel in combination with doxorubicin and cyclophosphamide (clinically important treatment related adverse events are presented).
- 300 gastric adenocarcinoma patients (221 patients in the phase III part of the study and 79 patients in the phase II part) who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment related adverse events are presented).
- 174 and 251 head and neck cancer patients who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment related adverse events are presented).

These reactions were described using the NCI Common Toxicity Criteria (grade 3 = G3; grade3-4 = G3/4; grade 4 = G4) and the COSTART terms. Frequencies are defined as: very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most commonly reported adverse reactions of docetaxel alone are: neutropenia (which was reversible and not

cumulative; the median day to nadir was 7 days and the median duration of severe neutropenia (<500 cells/mm^3) was 7 days), anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

For combination with trastuzumab, adverse events (all grades) reported in ≥ 10% are displayed. There was an increased incidence of SAEs (40% vs. 31%) and Grade 4 AEs (34% vs. 23%) in the trastuzumab combination arm compared to docetaxel monotherapy.

For combination with capecitabine, the most frequent treatment-related undesirable effects (≥ 5%) reported in a phase III study in breast cancer patients failing anthracycline treatment are presented (see capecitabine summary of product characteristics).

The following adverse reactions are frequently observed with docetaxel:

Immune system disorders

Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of docetaxel and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills. Severe reactions were characterised by hypotension and/or bronchospasm or generalized rash/erythema (see section 4.4).

Nervous system disorders

The development of severe peripheral neurotoxicity requires a reduction of dose (see sections 4.2 and 4.4). Mild to moderate neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

Skin and subcutaneous tissue disorders

Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the 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 lead to interruption or discontinuation of docetaxel treatment were reported (see sections 4.2 and 4.4). Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

General disorders and administration site conditions

Infusion site reactions were generally mild and consisted of hyper pigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasations and swelling of the vein.
Fluid retention includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity (see section 4.4).

Docetaxel 100mg/m² single agent

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Blood and the lymphatic system disorders	Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%);	Thrombocytopenia (G4: 0.2%)	

	Febrile neutropenia		
Immune system disorders	Hypersensivity (G3/4: 5.3%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%); Peripheral motor neuropathy (G3/4: 4%); Dysgeusia (severe 0.07%)		
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Vascular disorders		Hypotension; Hypertension; Haemorrhage	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (severe 2.7%)		
Gastrointestinal disorders	Stomatitis (G3/4: 5.3%); Diarrhoea (G3/4: 4%); Nausea (G3/4: 4%); Vomiting (G3/4: 3%)	Constipation (severe 0.2%); Abdominal pain (severe 1%); Gastrointestinal Haemorrhage (severe 0.3%)	Oesophagitis (severe: 0.4%)
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 5.9%); Nail disorders (severe 2.6%)		
Musculoskeletal, connective tissue disorders	Myalgia (severe 1.4%)	Arthralgia	
General disorders and administration site conditions	Fluid retention (severe: 6.5%); Asthenia (severe 11.2%); Pain	Infusion site reaction; Non-cardiac chest pain (severe 0.4%)	
Investigations		G3/4 Blood bilirubin increased (<5%); G3/4 Blood alkaline phosphatase increased (<4%); G3/4 AST increased (<3%); G3/4 ALT increased (<2%)	

Blood and Lymphatic system disorders
Rare: bleeding episodes associated with grade 3/4 thrombocytopenia.

Nervous system disorders
Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 100 mg/m² as single agent. The events were spontaneously reversible within 3 months.

Skin and subcutaneous tissue disorders
Very rare: one case of alopecia non-reversible at the end of the study. 73% of the cutaneous reactions were reversible within 21 days.

General disorders and administration site conditions
The median cumulative dose to treatment discontinuation was more than 1,000 mg/m^2 and the median time to fluid retention reversibility was 16.4 weeks (range 0 to 42 weeks). The onset of moderate and severe retention is delayed (median cumulative dose: 818.9 mg/m^2) in patients with premedication compared with patients without premedication (median cumulative dose: 489.7 mg/m^2); however, it has been reported in some patients during the early courses of therapy.

Docetaxel 75mg/m² single agent

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Infections (G3/4: 5%)	
Blood and the lymphatic system disorders	Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Immune system disorders		Hypersensitivity (no severe)
Metabolism and nutrition disorders	Anorexia	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Cardiac disorders		Arrhythmia (no severe);
Vascular disorders		Hypotension
Gastrointestinal disorders	Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhoea (G3/4: 1.7%)	Constipation
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 0.8%)	Nail disorders (severe 0.8%)
Musculoskeletal and connective tissue disorders		Myalgia
General disorders and administration site conditions	Asthenia (severe 12.4%); Fluid retention (severe 0.8%); Pain	
Investigations		G3/4 Blood bilirubin increased (<2%)

Docetaxel 75mg/m² in combination with doxorubicin

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 7.8%)		
Blood and lymphatic system disorders	Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)		
Immune system disorders		Hypersensitivity (G3/4: 1.2%)	
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Cardiac disorders		Cardiac failure; Arrhythmia (no severe)	
Vascular disorders			Hypotension
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhoea (G3/4: 6.2%); Vomiting (G3/4: 5%); Constipation		
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe 0.4%); Skin reaction (no severe)		
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions	Asthenia (severe 8.1%); Fluid retention (severe 1.2%); Pain	Infusion site reaction	
Investigations		G3/4 Blood bilirubin increased (<2.5%); G3/4 Blood alkaline phosphatase increased (<2.5%)	G3/4 AST increased (<1%); G3/4 ALT increased (<1%)

Docetaxel 75mg/m² in combination with cisplatin

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 5.7%)		
Blood and the lymphatic system disorders	Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%); Peripheral motor neuropathy (G3/4: 2%)		
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Vascular disorders		Hypotension (G3/4: 0.7%)	
Gastrointestinal disorders	Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%);	Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe 0.7%); Skin reaction (G3/4: 0.2%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe: 0.5%)		
General disorders and administration site conditions	Asthenia (severe 9.9%); Fluid retention (severe 0.7%); Fever (G3/4: 1.2%)	Infusion site reaction; pain	
Investigations		G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased (1.3%)	G3/4 AST increased (0.5%); G3/4 Blood alkaline phosphatase increased (0.3%)

Docetaxel 100mg/m² in combination with trastuzumab

MedDRA System Organ classes	**Very common adverse reactions ≥ 10 % of patients**	**Common adverse reactions ≥ 1 to < 10% of patients**
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%); Febrile neutropenia (includes neutropenia associated with fever and antibiotic use) or neutropenic sepsis	
Metabolism and nutrition disorders	Anorexia	
Psychiatric disorders	Insomnia	
Nervous system disorders	Paresthesia; Headache; Dysgeusia; Hypoaesthesia	
Eye disorders	Lacrimation increased; Conjunctivitis	
Cardiac disorders		Cardiac failure
Vascular disorders	Lymphoedema	
Respiratory, thoracic and mediastinal disorders	Epistaxis; Pharyngolaryngeal pain; Nasopharyngitis ; Dyspnoea; Cough; Rhinorrhoea	
Gastrointestinal disorders	Nausea; Diarrhoea; Vomiting; Constipation; Stomatitis; Dyspepsia; Abdominal pain	
Skin and subcutaneous tissue disorders	Alopecia; Erythema; Rash; Nail disorders	
Musculoskeletal and connective tissue disorders	Myalgia; Arthralgia; Pain in extremity; Bone pain; Back pain	
General disorders and administration site conditions	Asthenia; Oedema peripheral; Pyrexia; Fatigue; Mucosal inflammation; Pain; Influenza like illness; Chest pain; Chills	lethargy
Investigations	Weight increased	

Cardiac disorders

Symptomatic cardiac failure was reported in 2.2% of the patients who received docetaxel plus trastuzumab compared to 0% of patients given docetaxel alone. In the docetaxel plus trastuzumab arm, 64% had received a prior anthracycline as adjuvant therapy compared with 55% in the docetaxel arm alone.

Blood and the lymphatic system disorders

Very common: Haematological toxicity was increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m^2 is known to result in neutropenia in 97% of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

Docetaxel 75mg/m² in combination with capecitabine

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations		Oral candidiasis (G3/4: <1%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%); Decreased appetite	Dehydration (G3/4: 2%);
Nervous system disorders	Dysgeusia (G3/4: <1%); Paresthesia (G3/4: <1%)	Dizziness; Headache (G3/4: <1%); Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%)	Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%)
Gastrointestinal disorders	Stomatitis (G3/4: 18%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4: 2%); Dyspepsia	Abdominal pain upper; Dry mouth
Skin and subcutaneous tissue disorders	Hand-foot syndrome (G3/4: 24%) Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%)	Dermatitis; Rash erythematous (G3/4: <1%); Nail discolouration; Onycholysis (G3/4: 1%)
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%);
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4: 5%); Oedema peripheral	Lethargy; Pain

	(G3/4: 1%);	
Investigations		Weight decreased; G3/4 Blood bilirubin increased (9%)

Docetaxel 75mg/m² in combination with prednisone or prednisolone

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Infection (G3/4: 3.3%)	
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%); Anaemia (G3/4: 4.9%)	Thrombocytopenia (G3/4: 0.6%) Febrile neutropenia
Immune system disorders		Hypersensitivity (G3/4: 0.6%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G 3/4: 0.6%)
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%); Dyspnoea (G3/4: 0.6%); Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (no severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)	

Docetaxel 75mg/m² in combination with doxorubicin and cyclophosphamide

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 3.2%); Neutropenic infection. There were no septic deaths.		
Blood and the lymphatic system disorders	Anaemia (G3/4: 4.3%); Neutropenia (G3/4: 65.5%); Thrombocytopenia (G3/4: 2.0%); Febrile neutropenia		
Immune system disorders	Hypersensitivity (G3/4: 1.1%)		
Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)		
Nervous system disorders	Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebellar (G3/4: 0.1%)	Syncope (G3/4: 0%)
Eye disorders		Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)	
Cardiac disorders		Arrhythmia (G3/4: 0.1%), Congestive heart failure	
Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)
Respiratory, thoracic and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	Nausea (G3/4: 5.1%); Stomatitis (G3/4: 7.1%); Vomiting (G3/4: 4.3%); Diarrhoea (G3/4: 3.2%); Constipation (G3/4: 0.4%)	Abdominal pain (G3/4: 0.5%)	Colitis/enteritis/ large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia; Skin toxicity		

	(G3/4: 0.7%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 0.8%); Arthralgia (G3/4: 0.4%)		
Reproductive system and breast disorders	Amenorrhoea		
General disorders and administration site conditions	Asthenia (G3/4: 11%); Fever (G3/4: 1.2%); Oedema peripheral (G3/4: 0.4%)		
Investigations	Weight increased or decreased (G3/4: 0.3%)		

Cardiac disorder
Congestive Heart Failure (CHF) (2.3% at 70 months median follow-up) has also been reported. One patient in each treatment arm died due to cardiac failure.

Nervous system disorders
Peripheral sensory neuropathy was observed to be ongoing at the median follow-up time of 55 months in 9 patients out of the 73 patients with peripheral sensory neuropathy at the end of the chemotherapy.

Skin and subcutaneous tissue disorders
Alopecia was observed to be ongoing at the median follow-up time of 55 months in 22 patients out of the 687 patients with alopecia at the end of the chemotherapy.

General disorders and administration site conditions
Oedema peripheral was observed to be ongoing at the median follow-up time of 55 months in 18 patients out of the 112 patients with oedema peripheral at the end of the chemotherapy.

Reproductive system and breast disorders
Amenorrhoea was observed to be ongoing at the median follow-up time of 55 months in 133 patients out of the 233 patients with amenorrhoea at the end of the chemotherapy.

Docetaxel 75mg/m² in combination with cisplatin and 5-fluorouracil for gastric adenocarcinoma cancer:

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Neutropenic infection; Infection (G3/4: 11.7%).	
Blood and the lymphatic system disorders	Anaemia (G3/4: 20.9%); Neutropenia (G3/4: 83.2%); Thrombocytopenia (G3/4: 8.8%); Febrile neutropenia.	
Immune system disorders	Hypersensitivity	

	(G3/4: 1.7%).	
Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%)	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 8.7%).	Dizziness (G3/4: 2.3%); Peripheral motor neuropathy (G3/4: 1.3%).
Eye disorders		Lacrimation increased (G3/4: 0%).
Ear and labyrinth disorders		Hearing impaired (G3/4: 0%).
Cardiac disorders		Arrhythmia (G3/4: 1.0%).
Gastrointestinal disorders	Diarrhoea (G3/4: 19.7%); Nausea (G3/4: 16%); Stomatitis (G3/4: 23.7%); Vomiting (G3/4: 14.3%).	Constipation (G3/4: 1.0 %); Gastrointestinal pain (G3/4: 1.0%); Oesophagitis / dysphagia / odynophagia (G3/4: 0.7%).
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%).	Rash pruritus (G3/4: 0.7%); Nail disorders (G3/4: 0.7%); Skin exfoliation (G3/4: 0%).
General disorders and administration site conditions	Lethargy (G3/4: 19.0%); Fever (G3/4: 2.3%); Fluid retention (severe/life threatening: 1%).	

Blood and the lymphatic system disorders
Febrile neutropenia and neutropenic infection occurred in 17.2% and 13.5% of patients respectively, regardless of G-CSF use. G-CSF was used for secondary prophylaxis in 19.3% of patients (10.7% of the cycles). Febrile neutropenia and neutropenic infection occurred respectively in 12.1% and 3.4% of patients when patients received prophylactic G-CSF, in 15.6% and 12.9% of patients without prophylactic G-CSF, (see section 4.2).

Docetaxel 75mg/m² in combination with cisplatin and 5-fluorouracil for Head and Neck cancer

- Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 6.3%) Neutropenic infection		
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Cancer pain (G3/4: 0.6%)	

Blood and the lymphatic system disorders	Neutropenia (G3/4: 76.3%); Anaemia (G3/4: 9.2%); Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia	
Immune system disorders		Hypersensitivity (no severe)	
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		
Nervous system disorders	Dysgeusia/Parosmia; Peripheral sensory neuropathy (G3/4: 0.6%)	Dizziness	
Eye disorders		Lacrimation increased; Conjunctivitis	
Ear and labyrinth disorders		Hearing impaired	
Cardiac disorders		Myocardial ischemia (G3/4: 1.7%)	Arrhythmia (G3/4: 0.6%)
Vascular disorders		Venous disorder (G3/4: 0.6%)	
Gastrointestinal disorders	Nausea (G3/4: 0.6%) Stomatitis (G3/4: 4.0%) Diarrhoea (G3/4: 2.9%) Vomiting (G3/4: 0.6%)	Constipation; Oesophagitis/dysphagia/ Odynophagia (G3/4: 0.6%); Abdominal pain; Dyspepsia; Gastrointestinal haemorrhage (G3/4:0.6%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	Rash pruritus; Dry skin; Skin exfoliative (G3/4: 0.6%)	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.6%)	
General disorders and administration site conditions	Lethargy (G3/4: 3.4%); Pyrexia (G3/4: 0.6%); Fluid retention; Oedema		
Investigations		Weight increased	

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
Neoplasm benign, malignant and		Cancer pain (G3/4: 1.2%)	

unspecified (including cysts and polyps)			
Blood and the lymphatic system disorders	Neutropenia (G3/4: 83.5%); Anaemia (G3/4: 12.4); Thrombocytopenia (G3/4: 4.0%); Febrile neutropenia		
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
Nervous system disorders	Dysgeusia/Parosmia (G3/4: 0.4%); Peripheral sensory neuropathy (G3/4: 1.2%)	Dizziness (G3/4: 2.0%); Peripheral motor neuropathy (G3/4: 0.4%)	
Eye disorders		Lacrimation increased	Conjunctivitis
Ear and labyrinth disorders	Hearing impaired (G3/4: 1.2%)		
Cardiac disorders		Arrhythmia (G3/4: 2.0%)	Ischemia myocardial
Vascular disorders			Venous disorder
Gastrointestinal disorders	Nausea (G3/4: 13.9%); Stomatitis (G3/4: 20.7%); Vomiting (G3/4: 8.4%); Diarrhoea (G3/4: 6.8%); Oesophagitis/dysphagia/ Odynophagia (G3/4: 12.0%); Constipation (G3/4: 0.4%)	Dyspepsia (G3/4: 0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%); Rash pruritus;	Dry skin; Desquamation	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.4%)	
General disorders and administration site conditions	Lethargy (G3/4: 4.0%); Pyrexia (G3/4: 3.6%); Fluid retention (G3/4: 1.2%); Oedema (G3/4: 1.2%)		
Investigations	Weight decreased		Weight increased

Post-Marketing Experience

Neoplasm benign and malignant (including cysts and polyps)
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.

Blood and lymphatic system disorders
Bone marrow suppression and other haematologic adverse reactions have been reported. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has been reported.

Immune system disorders
Some cases of anaphylactic shock, sometimes fatal, have been reported.

Nervous system disorders
Rare cases of convulsion or transient loss of consciousness have been observed with docetaxel administration. These reactions sometimes appear during the infusion of the medicinal product.

Eye Disorders
Very rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during infusion of the medicinal product and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion. Cases of lacrimation with or without conjunctivitis, as cases of lachrymal duct obstruction resulting in excessive tearing have been rarely reported.

Ear and labyrinth disorders
Rare cases of ototoxicity, hearing impaired and/or hearing loss have been reported.

Cardiac disorder
Rare cases of myocardial infarction have been reported.

Vascular disorders
Venous thromboembolic events have rarely been reported.

Respiratory, thoracic and mediastinal disorders
Acute respiratory distress syndrome, interstitial pneumonia and pulmonary fibrosis have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Gastrointestinal disorders
Rare occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, colitis ischaemic, colitis and neutropenic enterocolitis have been reported. Rare cases of ileus and intestinal obstruction have been reported.

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

Skin and subcutaneous tissue disorders
Very rare cases of cutaneous lupus erythematous and bullous eruptions such as erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis, have been reported with docetaxel. In some cases concomitant factors may have contributed to the development of these effects. Sclerodermal-like changes usually preceded by peripheral lymphoedema have been reported with docetaxel.

General disorders and administration site conditions
Radiation recall phenomena have rarely been reported.
Fluid retention has not been accompanied by acute episodes of oliguria or hypotension. Dehydration and pulmonary oedema have rarely been reported.

4.9 Overdose

There were a few reports of overdose. There is no known antidote for docetaxel overdose. In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. In cases of overdose, exacerbation of adverse events may be expected. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose.

Other appropriate symptomatic measures should be taken, as needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD 02

Preclinical data

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

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

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some but not all cell lines over expressing the p-glycoprotein which is encoded by the multidrug resistance gene. *In vivo*, docetaxel is schedule independent and has a broad spectrum of experimental antitumour activity against advanced murine and human grafted tumours.

Clinical data

Breast cancer

Docetaxel in combination with doxorubicin and cyclophosphamide: adjuvant therapy

Data from a multicenter open label randomized study support the use of docetaxel for the adjuvant treatment of patients with operable node-positive breast cancer and KPS ≥ 80%, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either docetaxel 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2 (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion; all other medicinal products were given as intravenous bolus on day one. G-CSF was administered as secondary prophylaxis to patients who experienced complicated neutropenia (febrile neutropenia, prolonged neutropenia, or infection). Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 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. Incidence of relapses at 5 years was reduced in patients receiving TAC compared to those who received FAC (25% versus 32%, respectively) i.e. an absolute risk reduction by 7% (p=0.001). Overall survival at 5 years was also significantly increased with TAC compared to FAC (87% versus 81%, respectively) i.e. an absolute reduction of the risk of death by 6% (p=0.008). TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed:

		Disease Free Survival			Overall Survival		
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**P=**	**Hazard ratio***	**95% CI**	**P=**
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.70	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

*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 not proven in patients with 4 and more positive nodes (37% of the population) at the interim analysis stage. The effect appears to be less pronounced than in patients with 1-3 positive nodes. The benefit/risk ratio was not defined fully in patients with 4 and more positive nodes at this analysis stage.

Docetaxel as single agent

Two randomised phase III comparative studies, involving a total of 326 alkylating or 392 anthracycline failure metastatic breast cancer patients, have been performed with docetaxel at the recommended dose and regimen of 100 mg/m² every 3 weeks.

In alkylating-failure patients, docetaxel was compared to doxorubicin (75 mg/m² every 3 weeks). Without affecting overall survival time (docetaxel 15 months vs. doxorubicin 14 months, p=0.38) or time to progression (docetaxel 27 weeks vs. doxorubicin 23 weeks, p=0.54), docetaxel increased response rate (52% vs. 37%, p=0.01) and shortened time to response (12 weeks vs. 23 weeks, p=0.007). Three docetaxel patients (2%) discontinued the treatment due to fluid retention, whereas 15 doxorubicin patients (9%) discontinued due to cardiac toxicity (three cases of fatal congestive heart failure).

In anthracycline-failure patients, docetaxel was compared to the combination of mitomycin C and vinblastine (12 mg/m² every 6 weeks and 6 mg/m² every 3 weeks). Docetaxel increased response rate (33% vs. 12%, p<0.0001), prolonged time to progression (19 weeks vs. 11 weeks, p=0.0004) and prolonged overall survival (11 months vs. 9 months, p=0.01).

During these two phase III studies, the safety profile of docetaxel was consistent with the safety profile observed in phase II studies (see section 4.8).

An open-label, multicenter, randomized phase III study was conducted to compare docetaxel monotherapy and paclitaxel in the treatment of advanced breast cancer in patients whose previous therapy should have included an anthracycline. A total of 449 patients were randomized to receive either docetaxel monotherapy 100 mg/m² as a 1 hour infusion or paclitaxel 175 mg/m² as a 3 hour infusion. Both regimens were administered every 3 weeks.
Without affecting the primary endpoint, overall response rate (32% vs 25%, p=0.10), docetaxel prolonged median time to progression (24.6 weeks vs 15.6 weeks; p<0.01) and median survival (15.3 months vs 12.7 months; p=0.03).
More grade 3/4 adverse events were observed for docetaxel monotherapy (55.4%) compared to paclitaxel (23.0%).

Docetaxel in combination with doxorubicin

One large randomized phase III study, involving 429 previously untreated patients with metastatic disease, has been performed with doxorubicin (50 mg/m²) in combination with docetaxel (75 mg/m²) (AT arm) versus doxorubicin (60 mg/m²) in combination with cyclophosphamide (600 mg/m²) (AC arm). Both regimens were administered on day 1 every 3 weeks.

- Time to progression (TTP) was significantly longer in the AT arm versus AC arm, p=0.0138. The median TTP

was 37.3 weeks (95%CI:33.4 - 42.1) in AT arm and 31.9 weeks (95%CI : 27.4 - 36.0) in AC arm.

- Overall response rate (ORR) was significantly higher in the AT arm versus AC arm, p=0.009. The ORR was 59.3% (95%CI: 52.8 - 65.9) in AT arm versus 46.5% (95%CI : 39.8 - 53.2) in AC arm.

In this study, AT arm showed a higher incidence of severe neutropenia (90% versus 68.6%), febrile neutropenia (33.3% versus 10%), infection (8% versus 2.4%), diarrhoea (7.5% versus 1.4%), asthenia (8.5% versus 2.4%), and pain (2.8% versus 0%) than AC arm. On the other hand, AC arm showed a higher incidence of severe anaemia (15.8% versus 8.5%) than AT arm, and, in addition, a higher incidence of severe cardiac toxicity: congestive heart failure (3.8% versus 2.8%), absolute LVEF decrease ≥ 20% (13.1 % versus 6.1%), absolute LVEF decrease ≥ 30% (6.2% versus 1.1%). Toxic deaths occurred in 1 patient in the AT arm (congestive heart failure) and in 4 patients in the AC arm (1 due to septic shock and 3 due to congestive heart failure).
In both arms, quality of life measured by the EORTC questionnaire was comparable and stable during treatment and follow-up.

Docetaxel in combination with trastuzumab

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

Parameter	Docetaxel plus trastuzumab[1] n=92	Docetaxel[1] n=94
Response rate (95% CI)	61% (50-71)	34% (25-45)
Median Duration of response (months) (95% CI)	11.4 (9.2-15.0)	5.1 (4.4-6.2)
Median TTP (months) (95% CI)	10.6 (7.6-12.9)	5.7 (5.0-6.5)
Median Survival (months) (95% CI)	30.5[2] (26.8-ne)	22.1[2] (17.6-28.9)

TTP=time to progression; “ne” indicates that it could not be estimated or it was not yet reached.
1 Full analysis set (intent-to-treat)
2 Estimated median survival

Docetaxel in combination with capecitabine

Data from one multicenter, randomised, controlled phase III clinical study support the use of docetaxel in combination with capecitabine for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline. In this study, 255 patients were randomised to treatment with docetaxel (75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks) and capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by 1-week rest period). 256 patients were randomised to treatment with docetaxel alone (100 mg/ m^2 as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel + capecitabine combination arm (p=0.0126). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone).

The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (docetaxel + capecitabine) vs. 29.7% (docetaxel alone); p = 0.0058. Time to progressive disease was superior in the docetaxel + capecitabine combination arm (p<0.0001). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone).

Non-Small Cell Lung Cancer

Patients previously treated with chemotherapy with or without radiotherapy

In a phase III study, in previously treated patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 75 mg/m² compared to Best Supportive Care. The 1-year survival rate was also significantly longer in docetaxel (40%) versus BSC (16%).

There was less use of morphinic analgesic ($p<0.01$), non-morphinic analgesics ($p<0.01$), other disease related medications ($p=0.06$) and radiotherapy ($p<0.01$) in patients treated with docetaxel at 75 mg/m² compared to those with BSC.

The overall response rate was 6.8% in the evaluable patients, and the median duration of response was 26.1 weeks.

Docetaxel in combination with platinum agents in chemotherapy-naïve patients

In a phase III study, 1218 patients with unresectable stage IIIB or IV NSCLC, with KPS of 70% or greater, and who did not receive previous chemotherapy for this condition, were randomised to either Docetaxel (T) 75 mg/m^2 as a 1 hour infusion immediately followed by cisplatin (Cis) 75 mg/ m^2 over 30-60 minutes every 3 weeks (TCis), Docetaxel 75 mg/ m^2 as a 1 hour infusion in combination with carboplatin (AUC 6 mg/ml.min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25 mg/ m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/ m^2 administered on day 1 of cycles repeated every 4 weeks (VCis).

Survival data, median time to progression and response rates for two arms of the study are illustrated in the following table:

	TCis n=408	VCis N=404	Statistical Analysis
Overall Survival (Primary end-point):			
Median Survival (months)	11.3	10.1	Hazard Ratio: 1.122 [97.2% CI: 0.937; 1.342]*
1-year Survival (%)	46	41	Treatment difference: 5.4% [95% CI: -1.1; 12.0]
2-year Survival (%)	21	14	Treatment difference: 6.2% [95% CI: 0.2; 12.3]
Median Time to Progression (weeks)	22.0	23.0	Hazard Ratio: 1.032 [95% CI: 0.876; 1.216]
Overall Response Rate (%):	31.6	24.5	Treatment difference: 7.1% [95% CI: 0.7; 13.5]

*: Corrected for multiple comparisons and adjusted for stratification factors (stage of disease and region of treatment), based on evaluable patient population.

Secondary end-points included change of pain, global rating of quality of life by EuroQoL-5D, Lung Cancer Symptom Scale, and changes in Karnosfky performance status. Results on these end-points were supportive of the primary end-points results.

For docetaxel/carboplatin combination, neither equivalent nor non-inferior efficacy could be proven compared to the reference treatment combination VCis.

Prostate Cancer

The safety and efficacy of docetaxel in combination with prednisone or prednisolone in patients with hormone refractory metastatic prostate cancer were evaluated in a randomized multicenter Phase III study. A total of 1006 patients with KPS≥60 were randomized to the following treatment groups:

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

All 3 regimens were administered in combination with prednisone or prednisolone 5 mg twice daily, continuously.

Patients who received docetaxel every three weeks demonstrated significantly longer overall survival compared to those treated with mitoxantrone. The increase in survival seen in the docetaxel weekly arm was not statistically significant compared to the mitoxantrone control arm. Efficacy endpoints for the docetaxel arms versus the control arm are summarized in the following table:

Endpoint	*Docetaxel every 3 weeks*	*Docetaxel every week*	*Mitoxantrone every 3 weeks*
Number of patients	335	334	337
Median survival (months)	18.9	17.4	16.5
95% CI	(17.0-21.2)	(15.7-19.0)	(14.4-18.6)
Hazard ratio	0.761	0.912	--
95% CI	(0.619-0.936)	(0.747-1.113)	--
*p-value†**	0.0094	0.3624	--
Number of patients	291	282	300
*PSA**response rate (%)*	45.4	47.9	31.7
95% CI	(39.5-51.3)	(41.9-53.9)	(26.4-37.3)
*p-value**	0.0005	<0.0001	--
Number of patients Pain response rate (%)	153 34.6	154 31.2	157 21.7
95% CI	(27.1-42.7)	(24.0-39.1)	(15.5-28.9)
*p-value**	0.0107	0.0798	--
Number of patients	141	134	137
Tumor response rate (%)	12.1	8.2	6.6
95% CI	(7.2-18.6)	(4.2-14.2)	(3.0-12.1)
*p-value**	0.1112	0.5853	--

†Stratified log rank test
**Threshold for statistical significance=0.0175*
***PSA: Prostate-Specific Antigen*

Given the fact that docetaxel every week presented a slightly better safety profile than docetaxel every 3 weeks, it is possible that certain patients may benefit from docetaxel every week.

No statistical differences were observed between treatment groups for Global Quality of Life.

Gastric Adenocarcinoma

A multicenter, open-label, randomized study, was conducted to evaluate the safety and efficacy of docetaxel for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for metastatic disease. A total of 445 patients with KPS>70 were treated with either docetaxel (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and 5-fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm.
The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p=0.0004) in favour of the TCF arm. Overall survival was also significantly longer (p=0.0201) in favour of the TCF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarized in the following table:

Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

Endpoint	**TCF** n=221	**CF** N=224
Median TTP (months) (95%CI)	5.6 (4.86-5.91)	3.7 (3.45-4.47)
Hazard ratio (95% CI) *p-value	1.473 (1.189-1.825) 0.0004	
Median survival (months) (95% CI) 2-year estimate (%)	9.2 (8.38-10.58) 18.4	8.6 (7.16-9.46) 8.8
Hazard ratio (95% CI) *p-value	1.293 (1.041-1.606) 0.0201	
Overall Response Rate (CR+PR) (%)	36.7	25.4
p-value	0.0106	
Progressive Disease as Best Overall Response (%)	16.7	25.9

*Unstratified log rank test

Subgroup analyses across age, gender and race consistently favoured the TCF arm compared to the CF arm.

A survival update analysis conducted with a median follow-up time of 41.6 months no longer showed a statistically significant difference although always in favour of the TCF regimen and showed that the benefit of TCF over CF is clearly observed between 18 and 30 months of follow up.

Overall, quality of life (QoL) and clinical benefit results consistently indicated improvement in favour of the TCF arm. Patients treated with TCF had a longer time to 5% definitive deterioration of global health status on the QLQ-C30 questionnaire (p=0.0121) and a longer time to definitive worsening of Karnofsky performance status (p=0.0088) compared to patients treated with CF.

Head and neck cancer

- Induction chemotherapy followed by radiotherapy (TAX323)

  The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicenter, open-label, randomized study (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m2 followed by cisplatin (P) 75 mg/m2 followed by 5-fluorouracil (F) 750 mg/m2 per day as a continuous infusion for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. 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 for 7 weeks (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m2 followed by 5-fluorouracil (F) 1000 mg/m2 per day for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. 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 for 7 weeks (PF/RT). Locoregional therapy with radiation was delivered either with a conventional fraction (1.8 Gy - 2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy (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. Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. 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 also significantly longer in favor 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. Efficacy results are presented in the table below:

Efficacy of docetaxel in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	**Docetaxel + Cis+5-FU n=177**	**Cis+5-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	
Best overall response to chemotherapy (%) (95%CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response to study treatment [chemotherapy +/- radiotherapy] (%) (95%CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	
Median duration of response to chemotherapy ± radiotherapy (months) (95% CI)	n=128 15.7 (13.4-24.6)	n=106 11.7 (10.2-17.4)
Hazard ratio (95% CI) **p-value	0.72 (0.52-0.99) 0.0457	

A Hazard ratio of less than 1 favours docetaxel + cisplatin + 5-FU
*Cox model (adjustment for Primary tumour site, T and N clinical stages and PSWHO)
**Log rank test
*** Chi-square test

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

Clinical benefit parameters
The performance status scale, for head and neck (PSS-HN) subscales designed to measure understandability of speech, ability to eat in public, and normalcy of diet, was significantly in favour of TPF as compared to PF.
Median time to first deterioration of WHO performance status was significantly longer in the TPF arm compared to PF.
Pain intensity score improved during treatment in both groups indicating adequate pain management

- Induction chemotherapy followed by chemoradiotherapy (TAX324)
  The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a randomized, multicenter open-label, phase III, study (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of

0 or 1, were randomized to one of two arms. The study population comprised patients with technically unresectable disease, patients with low probability of surgical cure and patients aiming at organ preservation. The efficacy and safety evaluation solely addressed survival endpoints and the success of organ preservation was not formally addressed. Patients on the docetaxel arm received docetaxel (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of 5-fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of 5-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 intravenous 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 anytime following completion of CRT. All patients on the docetaxel-containing arm of the study received prophylactic antibiotics. The primary efficacy endpoint in this study, overall survival (OS) was significantly longer (log-rank test, p = 0.0058) with the docetaxel-containing regimen compared to PF (median OS: 70.6 versus 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) with an overall median follow up time of 41.9 months. 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 docetaxel in the induction treatment of patients with locally advanced SCCHN (Intent-to-Treat Analysis)

Endpoint	**Docetaxel +Cis+5-FU n=255**	**Cis+5-FU n=246**
Median overall survival (months) (95%CI)	70.6 (49.0-NA)	30.1 (20.9-51.5)
Hazard ratio (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	
Median PFS (months) (95% CI)	35.5 (19.3-NA)	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 +/- radiotherapy] (%) (95%CI)	76.5 (70.8-81.5)	71.5 (65.5-77.1)
***p-value	0.209	

A Hazard ratio of less than 1 favours docetaxel + cisplatin + fluorouracil
* Un-adjusted log-rank test
** Un-adjusted log-rank test, not adjusted for multiple comparisons
*** Chi-square test, not adjusted for multiple comparisons
NA-not applicable

5.2 Pharmacokinetic properties

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in Phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the α, β and γ phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100 mg/m^2 dose given as a one hour infusion a mean peak plasma level of 3.7 μg/ml was obtained with a corresponding AUC of 4.6 h.μg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m^2 and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

A study of ^{14}C-docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and faeces following cytochrome P450-mediated oxidative metabolism of the tert-butyl ester group, within seven days, the urinary and faecal excretion accounted for about 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in faeces is excreted during the first 48 hours as one major inactive metabolite and 3 minor inactive metabolites and very low amounts of unchanged medicinal product.

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

When used in combination, docetaxel does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their coadministration.

Phase I study evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of docetaxel (C_{max} and AUC) and no effect by docetaxel on the pharmacokinetics of a relevant capecitabine metabolite 5'-DFUR.

Clearance of docetaxel in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after docetaxel infusion is similar to that observed with cisplatin alone.

The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumours had no influence on the pharmacokinetics of each individual drug.

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.

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

Docetaxel has been shown to be mutagenic in the *in vitro* micronucleus and chromosome aberration test in CHO-K1 cells and in the *in vivo* micronucleus test in the mouse. However, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. These results are consistent with the pharmacological activity of docetaxel.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder vial:
- povidone K-12 (E1201)
- hydroxypropylbetadex
- glucose monohydrate.

Solvent vial:
- water for injections

6.2 Incompatibilities

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

6.3 Shelf life

- 24 months

- Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours when stored either at room temperature (below 25°C) or between 2°C and 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions. The premix is for single use only.

- Diluted solution: the infusion solution may contain from approximately 0.3 mg/ml to a maximum of 0.74 mg/ml docetaxel in either 5% glucose for injection or 0.9% sodium chloride solution. Chemical and physical in-use stability has been demonstrated for 4 hours when stored at room temperature (below 25°C) and 24 hours when stored at between 2°C and 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.
Store in the original package in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

The vials are supplied in cartons each containing two vials.
Each carton pack contains:
- One single-dose vial of docetaxel powder for solution for infusion and,
- One single-dose vial of solvent.

<u>Docetaxel 80 mg powder for concentrate for solution for infusion vial</u>

Injection vial 50 ml colourless, tubular glass type I with bromobutyl rubber stopper, aluminium seal and polypropylene snap-cap.

This vial contains 80 mg of docetaxel with povidone K-12, hydroxypropylbetadex and glucose monohydrate as excipients (fill volume 81.5 mg/16.3 ml).This fill volume has been established during the development for the ease of

withdrawing 16.0 ml of reconstituted solution. This overfill ensures that after reconstitution with 13.4 ml of the accompanying solvent for Docetaxel 80 mg vial, there is a minimal extractable reconstituted volume of 16 ml containing 5 mg/ml docetaxel which corresponds to the labelled amount of 80 mg per vial.

Solvent for Docetaxel 80 mg powder for concentrate for solution for infusion vial

Injection vial 20 R colourless, tubular glass type I with chlorobutyl rubber stopper, aluminium seal and polypropylene snap-cap.

Solvent vial contains 13.4 ml in water for injections (fill volume: 13.9 ml). The addition of 13.4 ml of the solvent vial to the contents of the Docetaxel 80 mg powder for solution for infusion vial ensures a reconstituted concentration of 5 mg/ml docetaxel.

6.6 Special precautions for disposal

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

If Docetaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Docetaxel concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation for the intravenous administration

a) *Preparation of the Docetaxel 80 mg reconstituted solution (5 mg docetaxel/ml)*

If the vials are stored under refrigeration, allow the required number of Docetaxel 80 mg boxes to stand at room temperature (below 25°C) for 5 minutes.

Using a syringe fitted with a needle, aseptically withdraw 13.4 ml of the solvent for Docetaxel 80 mg vial by partially inverting the vial.

Inject the entire contents of the syringe into the corresponding Docetaxel 80 mg vial.

Remove the syringe and needle and mix manually by repeated inversions until all powder is dissolved (within 5 minutes).

Visually check that the solution is homogeneous, clear and free from visible particles.

b) *Preparation of the infusion solution*

More than one reconstituted vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding reconstituted volume containing 5 mg/ml docetaxel from the appropriate number of reconstituted vials using graduated syringes fitted with a needle. For example, a dose of 100 mg docetaxel would require 20 ml docetaxel reconstituted solution.

Inject the required premix volume into a 250 ml non-PVC infusion bag or glass bottle containing either 5% glucose solution or 0.9% sodium chloride solution.

If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

Mix the infusion bag or bottle manually using a rocking motion.

The solution should be aseptically administered as a 1-hour infusion under room temperature (below 25°C) and normal lighting conditions.

As with all parenteral products, Docetaxel 80 mg reconstituted solution and infusion solution should be visually

inspected prior to use, solutions containing a precipitate should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 1557/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th July 2012

10 DATE OF REVISION OF THE TEXT