1. NAME OF THE MEDICINAL PRODUCT

DOCETAXEL EBEWE 10 mg/ml

Concentrate for solution for infusion

WARNINGS

Docetaxel Ebewe concentrate for solution for infusion should be administered under the supervision of a physician experienced in the use of antineoplastic agents.

WARNING: TOXIC DEATHS, HEPATOTOXICITY, NEUTROPENIA, HYPERSENSITIVITY REACTIONS, and FLUID RETENTION

The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m^2.

Docetaxel should not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 × ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of docetaxel therapy.

Docetaxel therapy should not be given to patients with neutrophil counts of < 1,500 cells/mm. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving docetaxel.

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received a 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and administration of appropriate therapy. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80 (see section 4.3 "Contraindications").

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of the concentrate for solution for infusion contains 10 mg Docetaxel.
One vial of concentrate for solution for infusion contains Docetaxel as a trihydrate corresponding to 20 mg, 80 mg & 160 mg of Docetaxel (anhydrous).
Each vial of 2 ml contains 20 mg Docetaxel (10 mg/ml).
Each vial of 8 ml contains 80 mg Docetaxel (10 mg/ml).
Each vial of 16 ml contains160 mg Docetaxel (10 mg/ml).
Excipient: Each single-dose vial of concentrate for solution contains 27% (w/w) ethanol 96%.
For a full list of excipients, see section 6.1: "List of Excipients".

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
Clear, colorless to pale, yellow solution; pH 3.0 – 4.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer:
Docetaxel Ebewe in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.
Docetaxel Ebewe 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 Ebewe monotherapy is indicated for the treatment of patients with metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.
Docetaxel Ebewe in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2 and who previously have not received chemotherapy for metastatic disease.
Docetaxel Ebewe in combination with capecitabine is indicated for the treatment of patients with metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Doxorubicin and cyclophosphamide followed by Docetaxel Ebewe in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with HER2 overexpressing, node-positive or high-risk node-negative breast cancer.
Docetaxel Ebewe in combination with trastuzumab, and carboplatin (TCH) is indicated for the adjuvant treatment of patients with HER2 overexpressing, node-positive or high-risk node-negative breast cancer.

Non-small cell lung cancer:
Docetaxel Ebewe is indicated for the treatment of patients with advanced non-small cell lung carcinoma.

Ovarian cancer:
Docetaxel Ebewe is indicated for treatment of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.

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

Esophageal cancer:
Docetaxel Ebewe is also indicated for the treatment of esophageal cancer.

Gastric cancer:
Docetaxel Ebewe is also indicated for the treatment of advanced gastric cancer.

Head and neck cancer (SCCHN):
Docetaxel Ebewe as monotherapy is indicated in the treatment of patients with recurrent and/or metastasis squamous cell carcinoma of the head and neck after failure of a previous chemotherapy regimen.
Docetaxel Ebewe 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.

Additional Therapeutic Activity Ovarian Cancer:
Docetaxel Ebewe in combination with carboplatin is used for treatment of patients with advanced carcinoma of the ovary who have not previously received cytotoxic therapy for this condition. Recommended doses are carboplatin AUC 5 plus Docetaxel Ebewe 75 mg/m^2.

4.2 Posology and method of administration

The use of docetaxel should be confined to units specialized 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: "Special precautions for disposal and other handling").

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 Ebewe administration, unless contraindicated, can be used (see section 4.4). Prophylactic G-CSF may be used to mitigate the risk of hematological 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 Ebewe infusion (see section 6.6: "Special warnings and precautions for use").
Docetaxel Ebewe is administered as a one-hour infusion every three weeks.
For further details on preparation of infusion solution see section "Special precautions for disposal and other handling".
Care should be taken of administration of the infusion to avoid extravasation.

Breast cancer

As adjuvant treatment of operable node-positive breast cancer, the recommended dose of Docetaxel Ebewe 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 Ebewe is 100 mg/m^2 as monotherapy. In first-line treatment, Docetaxel Ebewe 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).
In combination with trastuzumab the recommended dose of Docetaxel Ebewe is 100 mg/m^2 every three weeks, with trastuzumab administered weekly. In the pivotal trial 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 dose and administration, see trastuzumab "Summary of product characteristics".
In combination with capecitabine, the recommended dose of Docetaxel Ebewe 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".

In the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2 the recommended docetaxel dose is as follows:

- AC-TH:
  AC (cycles 1 - 4): doxorubicin (A) 60 mg/m^2 followed by cyclophosphamide (C) 600 mg/m^2 administered every three weeks for 4 cycles.
  TH (cycles 5 - 8): docetaxel (T) 100 mg/m^2 administered every three weeks for 4 cycles, and trastuzumab (H) administered weekly according the following schedule:
- Cycle 5 (starting three weeks after the last cycle of AC):
  Day 1: trastuzumab 4 mg/kg (loading dose)
  Day 2: docetaxel 100 mg/m^2
  Days 8 and 15: trastuzumab 2 mg/kg
- Cycles 6 - 8:
  Day 1: docetaxel 100 mg/m^2 and trastuzumab 2 mg/kg
  Days 8 and 15: trastuzumab 2 mg/kg
  Three weeks after day 1 of cycle 8: trastuzumab 6 mg/kg is given every three weeks.
  Trastuzumab is administered for a total duration of 1 year.
- TCH:
  TCH (cycles 1 - 6): docetaxel (T) 75 mg/m^2 and carboplatin (C) at AUC of 6 mg/mL/min administered every three weeks and trastuzumab (H) administered weekly according the following schedule:
- Cycle 1:
  Day 1: trastuzumab 4 mg/kg (loading dose)
  Day 2: docetaxel 75 mg/m^2 and carboplatin at AUC of 6 mg/mL/min
  Days 8 and 15: trastuzumab 2 mg/kg
- Cycles 2-6:
  Day 1: docetaxel 75 mg/m^2 followed by carboplatin at AUC of 6 mg/mL/min and trastuzumab 2 mg/kg
  Days 8 and 15: trastuzumab 2 mg/kg
  Three weeks after day 1 of cycle 6: trastuzumab 6 mg/kg is given every three weeks.
  Trastuzumab is administered for a total duration of 1 year.

Non-small cell lung cancer

In chemotherapy-naïve patients treated for non-small cell lung cancer, the recommended dose regimen is Docetaxel Ebewe 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 dose is 75 mg/m^2 as a single agent.

Prostate cancer

The recommended dose of Docetaxel Ebewe is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously (see section 5.1: "Pharmacodynamic properties").

Gastric adenocarcinoma

The recommended dose of Docetaxel Ebewe 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 hematological 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 hematological toxicities. All patients on the docetaxel-containing arm of the TAX 323 and TAX 324 studies 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 1,000 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 Ebewe should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during Docetaxel Ebewe therapy, the dose of Docetaxel Ebewe should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

Adjuvant therapy for breast cancer

Primary G-CSF prophylaxis should be considered in patients who receive docetaxel, doxorubicin and cyclophosphamide (TAC) adjuvant therapy for breast cancer. Patients who experience febrile neutropenia and/or neutropenic infection should have their docetaxel dose reduced to 60 mg/m^2 in all subsequent cycles (see sections 4.4: "Special warnings and precautions for use" and 4.8: "Undesirable effects"). Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60 mg/m^2.

In combination with cisplatin

For patients who are dosed initially at Docetaxel Ebewe 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-hematologic toxicities, the Docetaxel Ebewe dose in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dose 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 Ebewe/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 Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with Docetaxel Ebewe 55 mg/m^2.
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the Docetaxel Ebewe 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 Ebewe dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur, the Docetaxel Ebewe dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia, the Docetaxel Ebewe dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of Docetaxel Ebewe 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: "Special warnings and precautions for use").

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

Toxicity	Dose adjustment
Diarrhea grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce Docetaxel Ebewe dose by 20%.
Diarrhea grade 4	First episode: reduce Docetaxel Ebewe 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 Ebewe dose by 20%.
Stomatitis/mucositis grade 4	First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce Docetaxel Ebewe dose by 20%.

For cisplatin and 5-fluorouracil dose adjustments, see the corresponding "Summary of product characteristics".
In the pivotal SCCHN trials patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g., days 6-15) in all subsequent cycles.

Special populations:

Patients with hepatic impairment

Based on pharmacokinetic data with docetaxel at 100 mg/m^2 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 trial 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 for the other indications.

Paediatric population

The safety and efficacy of docetaxel in nasopharyngeal carcinoma in children aged 1 month to less than 18 years have not yet been established. There is no relevant use of docetaxel in the paediatric population in the indications breast cancer, non-small cell lung cancer, prostate cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma.

Older people

Based on pharmacokinetic analysis of this population, 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 Ebewe must not be used in patients with baseline neutrophil count of < 1,500 cells/mm^3.
- Docetaxel Ebewe must not be used in patients with severe liver impairment since there is no data available (see sections 4.2: "Posology and method of administration" and 4.4: "Special warnings and precautions for use").
- 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: "Posology and method of administration").

Hematology

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 "Posology and method of administration"). 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: "Posology and method of administration").
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: "Posology and method of administration" and 4.8: "Undesirable effects").
In patients treated with docetaxel in combination with doxorubicin and cyclophosphamide (TAC), febrile neutropenia and/or neutropenic infection occurred at lower rates when patients received primary G-CSF prophylaxis. Primary G-CSF prophylaxis should be considered in patients who receive adjuvant therapy with TAC for breast cancer to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TAC should be closely monitored (see sections 4.2: "Posology and method of administration" and 4.8: "Undesirable effects").

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 localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalized rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Cutaneous reactions

Localized skin erythema of the extremities (palms of the hands and soles of the feet) with edema 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 "Posology and method of administration").

Fluid retention

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

Respiratory disorders

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

Patients with liver impairment

In patients treated with docetaxel at 100 mg/m^2 as a 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 hemorrhage 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 "Posology and method of administration").
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 trial 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.

Patients with renal impairment

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

Nervous system

The development of severe peripheral neurotoxicity requires a reduction of dose (see section 4.2: "Posology and method of administration").

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 "Undesirable Effects").
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.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. 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 (see section 4.8: "Undesirable effects").

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: "Fertility, pregnancy and lactation").
The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see section 4.5: "Interaction with other medicinal products and other forms of interaction").

Additional cautions for use in adjuvant treatment of breast cancer

Complicated neutropenia

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

Gastrointestinal reactions

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

Congestive heart failure

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow-up period. In patients treated with the TAC regimen for node-positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see sections 4.8: "Undesirable effects" and 5.1: "Pharmacodynamic properties").

Leukemia

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

Patients with 4+ nodes

As the benefit observed in patients with 4+ nodes was not statistically significant on disease-free survival (DFS) and overall survival (OS), the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis (see section 5.1: "Pharmacodynamic properties").

Older people

There are limited 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, diarrhea, anorexia, and peripheral edema occurred at rates ≥ 10 percentage 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 patients 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. Older patients treated with TCF should be closely monitored.

Excipients

Docetaxel Ebewe contains 27 vol % ethanol (alcohol); i.e., 160 mg (average dose) contains 4100 mg alcohol, equivalent to less than 100 ml beer.
Harmful for those who are suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or other diseases or epilepsy.
Consideration should be given to possible effects on the central nervous system.
The amount of alcohol in this medicinal product may alter the effects of other medicines.
The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.

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 metabolized by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as cyclosporine, 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.
In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor (see section 4.4: "Posology and method of administration"). In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49%.
Docetaxel pharmacokinetics in the presence of prednisone was studied in patients with metastatic prostate cancer. Docetaxel is metabolized by CYP3A4 and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the pharmacokinetics of docetaxel was observed.
Docetaxel is highly protein-bound (> 95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medication 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 with docetaxel, the clearance of carboplatin was about 50% higher than values previously reported for carboplatin monotherapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Breast-feeding

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.

Contraception in males and females

An effective method of contraception should be used during treatment.

Fertility

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.

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.
The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile for all indications
The adverse reactions considered to be possibly or probably related to the administration of docetaxel have been obtained in:

- 1,312 and 121 patients who received 100 mg/m^2 and 75 mg/m^2 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).
- 1,276 patients (744 and 532 in TAX 316 and GEICAM 9805, respectively) 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; grade 3-4 = G3/4; grade 4 = G4) and the COSTART terms.
Frequencies are defined as very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from 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), anemia, alopecia, nausea, vomiting, stomatitis, diarrhea 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 trial 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: "Posology and method of administration").

Nervous system disorders
The development of severe peripheral neurotoxicity requires a reduction of dose (see sections 4.2: "Posology and method of administration" and section 4.4 "Special warnings and precautions"). Mild to moderate neuro-sensory signs are characterized by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterized by weakness.

Skin and subcutaneous tissue disorders
Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterized by a rash including localized 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 "Posology and method of administration" and "Special warnings and precautions for use"). Severe nail disorders are characterized by hypo- or hyperpigmentation and sometimes pain and onycholysis.

General disorders and administration site conditions
Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.
Fluid retention includes events such as peripheral edema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. The peripheral edema usually starts at the lower extremities and may become generalized with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity (see section 4.4: "Special warnings and precautions").

Tabulated List of adverse reactions in breast cancer for DOCETAXEL 100 mg/m^2 single agent

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients	Uncommon adverse reactions ≥ 0.1 to < 1% of patients
Investigations		G3/4 Blood bilirubin increased (< 5%); G3/4 Blood alkaline phosphatase increased (< 4%); G3/4 AST increased (< 3%); G3/4 ALT increased (< 2%)	
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Blood and lymphatic system disorders	Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%); Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%); Peripheral motor neuropathy (G3/4: 4%); Dysgeusia (severe: 0.07%)		
Respiratory, thoracic and mediastinal disorders	Dyspnoea (severe: 2.7%)		
Gastrointestinal disorders	Stomatitis (G3/4: 5.3%); Diarrhea (G3/4: 4%); Nausea (G3/4: 4%); Vomiting (G3/4: 3%)	Constipation (severe: 0.2%); Abdominal pain (severe: 1%); Gastrointestinal hemorrhage (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 and connective tissue disorders	Myalgia (severe: 1.4%)	Arthralgia	
Metabolism and nutrition disorders	Anorexia		
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%)	
Vascular disorders		Hypotension; Hypertension; Hemorrhage	
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%)	
Immune system disorders	Hypersensitivity (G3/4: 5.3%)		

Description of selected adverse reactions in breast cancer for docetaxel 100 mg/ m^2 single agent
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/m^2 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.

Tabulated List of adverse reactions in non-small cell lung cancer for DOCETAXEL 75 mg/m^2 single agent

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients
Investigations		G3/4 Blood bilirubin increased (< 2%)
Cardiac disorders		Arrhythmia (no severe)
Blood and lymphatic system disorders	Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Gastrointestinal disorders	Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhea (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
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infections (G3/4: 5%)	
Vascular disorders		Hypotension
General disorders and administration site conditions	Asthenia (severe: 12.4%); Fluid retention (severe: 0.8%); Pain	
Immune system disorders		Hypersensitivity (no severe)

Tabulated List of adverse reactions in breast cancer for DOCETAXEL 75 mg/m^2 in combination with doxorubicin

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients	Uncommon adverse reactions ≥ 0.1 to < 1% of patients
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%)
Cardiac disorders		Cardiac failure; Arrhythmia (no severe)	
Blood and lymphatic system disorders	Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)		
Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhea (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	
Metabolism and nutrition disorders		Anorexia	
Infections and infestations	Infection (G3/4: 7.8%)		
Vascular disorders			Hypotension
General disorders and administration site conditions	Asthenia (severe: 8.1%); Fluid retention (severe: 1.2%); Pain	Infusion site reaction	
Infusion site reaction Immune system disorders		Hypersensitivity (G3/4: 1.2%)	

Tabulated List of adverse reactions in non-small cell lung cancer for DOCETAXEL 75 mg/m^2 in combination with cisplatin

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients	Uncommon adverse reactions ≥ 0.1 to < 1% of patients
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%)
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Blood and lymphatic system disorders	Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%); Peripheral motor neuropathy (G3/4: 2%)		
Gastrointestinal disorders	Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhea (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%)		
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infection (G3/4: 5.7%)		
Vascular disorders		Hypotension (G3/4: 0.7%)	
General disorders and administration site conditions	Asthenia (severe: 9.9%); Fluid retention (severe: 0.7%); Fever (G3/4: 1.2%)	Infusion site reaction; Pain	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		

Tabulated List of adverse reactions in breast cancer for DOCETAXEL 100 mg/m^2 in combination with trastuzumab

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients
Investigations	Weight increased	
Cardiac disorders		Cardiac failure
Blood and lymphatic system disorders	Neutropenia (G3/4: 32%); Febrile neutropenia (includes neutropenia associated with fever and antibiotic use) or neutropenic sepsis	
Nervous system disorders	Paresthesia; Headache; Dysgeusia; Hypoesthesia	
Eye disorders	Lacrimation increased; Conjunctivitis	
Respiratory, thoracic and mediastinal disorders	Epistaxis; Pharyngolaryngeal pain; Nasopharyngitis; Dyspnoea; Cough; Rhinorrhoea	
Gastrointestinal disorders	Nausea; Diarrhea; 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	
Metabolism and nutrition disorders	Anorexia	
Vascular disorders	Lymphoedema	
General disorders and administration site conditions	Asthenia; Oedema peripheral; Pyrexia; Fatigue; Mucosal inflammation; Pain; Influenza like illness; Chest pain; Chills	Lethargy
Psychiatric disorders	Insomnia	

Description of selected adverse reactions in breast cancer for DOCETAXEL 100 mg/m^2 in combination with trastuzumab
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 lymphatic system disorders
Very common: Hematological 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 100 mg/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).

Tabulated List of adverse reactions in breast cancer for DOCETAXEL 75 mg/m^2 in combination with capecitabine

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients
Investigations		Weight decreased; G3/4 Blood bilirubin increased (9%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Nervous system disorders	Dysgeusia (G3/4: < 1%); Paraesthesia (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%); Diarrhea (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%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%); Decreased appetite	Dehydration (G3/4: 2%)
Infections and infestations		Oral candidiasis (G3/4: < 1%)
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/weakness (G3/4: 5%); Oedema peripheral (G3/4: 1%)	Lethargy; Pain

Tabulated List of adverse reactions in prostate cancer for DOCETAXEL 75 mg/m^2 in combination with prednisone or prednisolone

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 32%); Anaemia (G3/4: 4.9%)	Thrombocytopenia (G3/4: 0.6%); Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G3/4: 0.6%)
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%); Diarrhea (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 bone disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Infections and infestations	Infection (G3/4: 3.3%)	
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe: 0.6%)	
Immune system disorders		Hypersensitivity (G3/4: 0.6%)

Tabulated List of adverse reactions for adjuvant therapy with DOCETAXEL 75 mg/m^2 in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316) and node-negative (GEICAM 9805) breast cancer - pooled data

MedDRA System Organ classes	Very common adverse reactions ≥ 10% of patients	Common adverse reactions ≥ 1 to < 10% of patients	Uncommon adverse reactions ≥ 0.1 to < 1% of patients
Infections and infestations	Infection (G3/4: 2.4%); Neutropenic infection (G3/4: 2.6%)		
Blood and lymphatic system disorders	Anaemia (G3/4: 3%); Neutropenia (G3/4: 59.2%); Thrombocytopenia (G3/4: 1.6%); Febrile neutropenia (G3/4: NA)		
Immune system disorders		Hypersensitivity (G3/4: 0.6%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 1.5%)		
Nervous system disorders	Dysgeusia (G3/4: 0.6%); Peripheral sensory neuropathy (G3/4: 0.1%)	Peripheral motor neuropathy (G3/4: 0%)	Syncope (G3/4: 0%); Neurotoxicity (G3/4: 0%); Somnolence (G3/4: 0%)
Eye disorders	Conjunctivitis (G3/4: < 0.1%)	Lacrimation increased (G3/4: < 0.1%)	
Cardiac disorders		Arrhythmia (G3/4: 0.2%)	
Vascular disorders	Hot flush (G3/4: 0.5%)	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%); Stomatitis (G3/4: 6%); Vomiting (G3/4: 4.2%); Diarrhoea (G3/4: 3.4%); Constipation (G3/4: 0.5%)	Abdominal pain (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (persisting < 3%); Skin disorder (G3/4: 0.6%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 0.7%); Arthralgia (G3/4: 0.2%)		
Reproductive system and breast disorders	Amenorrhoea (G3/4: NA)		
General disorders and administration site conditions	Asthenia (G3/4: 10%); Pyrexia (G3/4: NA); Oedema peripheral (G3/4: 0.2%)		
Investigations		Weight increased (G3/4: 0%); Weight decreased (G3/4: 0.2%)	

Description of selected adverse reactions for adjuvant therapy with Docetaxel 75 mg/m^2 in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316) and node-negative (GEICAM 9805) breast cancer
Nervous system disorders
Peripheral sensory neuropathy was observed to be ongoing during follow-up in 10 patients out of the 84 patients with peripheral sensory neuropathy at the end of the chemotherapy in the node-positive breast cancer study (TAX 316).
Cardiac disorders
In study TAX 316, 26 patients (3.5%) in the TAC arm and 17 patients (2.3%) in the FAC arm experienced congestive heart failure. All except one patient in each arm were diagnosed with CHF more than 30 days after the treatment period. Two patients in the TAC arm and 4 patients in the FAC arm died because of cardiac failure.
In GEICAM 9805 study, 3 patients (0.6%) in TAC arm and 3 patients (0.6%) in FAC arm developed congestive heart failure during the follow-up period. One patient in TAC arm died because of dilated cardiomyopathy.
Skin and subcutaneous tissue disorders
In study TAX 316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 of 744 TAC patients and 645 of 736 FAC patients.
At the end of the follow-up period (actual median follow-up period of 96 months), alopecia was observed to be ongoing in 29 TAC patients (3.9%) and 16 FAC patients (2.2%).
In GEICAM 9805 study, alopecia persisted into the follow-up period (median follow-up time of 10 years and 5 months) and was observed to be ongoing in 49 patients (9.2%) in TAC arm and 35 patients (6.7%) in FAC arm. Alopecia related to study drug started or worsened during the follow-up period in 42 patients (7.9%) in TAC arm and 30 patients (5.8%) in FAC arm.
Reproductive system and breast disorders
Amenorrhoea was observed to be ongoing during follow-up in 121 patients out of the 202 patients with amenorrhoea at the end of the chemotherapy in study TAX 316.
In GEICAM 9805 study, amenorrhoea persisted into the follow-up period (median follow-up time of 10 years and 5 months) and was observed to be ongoing in 18 patients (3.4%) in TAC arm and 5 patients (1.0%) in FAC arm.
General disorders and administration site conditions
In study TAX 316, peripheral oedema was observed to be ongoing in 19 patients out of the 119 patients with peripheral oedema in the TAC arm and 4 patients out of the 23 patients with peripheral oedema in the FAC arm.
In study GEICAM 9805, lymphoedema was observed to be ongoing in 4 of the 5 patients in TAC arm and in 1 of the 2 patients in FAC arm at the end of the chemotherapy and did not resolve during the follow-up period (median follow-up time of 10 years and 5 months). Asthenia persisted into the follow-up period (median follow-up time of 10 years and 5 months) and was observed to be ongoing in 12 patients (2.3%) in TAC arm and 4 patients (0.8%) in FAC arm.
Acute leukaemia/Myelodysplastic syndrome
After 10 years of follow-up in study TAX 316, acute leukaemia was reported in 4 of 744 TAC patients and in 1 of 736 FAC patients. Myelodysplastic syndrome was reported in 2 of 744 TAC patients and in 1 of 736 FAC patients.
After 10 years of follow-up in GEICAM 9805 study, acute leukaemia occurred in 1 of 532 (0.2%) patients in TAC arm. No cases were reported in patients in FAC arm. No patient was diagnosed with myelodysplastic syndrome in either treatment group.

Neutropenic complications

Table below shows that the incidence of Grade 4 neutropenia, febrile neutropenia and neutropenic infection was decreased in patients who received primary G-CSF prophylaxis after it was made mandatory in the TAC arm – GEICAM study.

Neutropenic complications in patients receiving TAC with or without primary G-CSF prophylaxis (GEICAM 9805)

	Without primary G-CSF prophylaxis (n = 111) n (%)	With primary G-CSF prophylaxis (n = 421) n (%)
Neutropenia (Grade 4)	104 (93.7)	135 (32.1)
Febrile neutropenia	28 (25.2)	23 (5.5)
Neutropenic infection	14 (12.6)	21 (5.0)
Neutropenic infection (Grade 3-4)	2 (1.8)	5 (1.2)

Tabulated List of adverse reactions in gastric adenocarcinoma cancer for DOCETAXEL 75 mg/m² in combination with cisplatin and 5-fluorouracil

MedDRA System Organ classes	**Very common adverse reactions ≥ 10% of patients**	**Common adverse reactions ≥ 1 to < 10% of patients**
Cardiac disorders		Arrhythmia (G3/4: 1.0%)
Blood and lymphatic system disorders	Anaemia (G3/4: 20.9%); Neutropenia (G3/4: 83.2%); Thrombocytopenia (G3/4: 8.8%); Febrile neutropenia	
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%)
Gastrointestinal disorders	Diarrhea (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%)
Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%)	
Infections and infestations	Neutropenic infection; Infection (G3/4: 11.7%)	
General disorders and administration site conditions	Lethargy (G3/4: 19.0%); Fever (G3/4: 2.3%); Fluid retention (severe/life threatening: 1%)	
Immune system disorders	Hypersensitivity (G3/4: 1.7%)	

Description of selected adverse reactions in gastric adenocarcinoma cancer for Docetaxel 75 mg/m² in combination with cisplatin and 5-fluorouracil

Blood and 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: "Posology and method of administration").

Tabulated List of adverse reactions in head and neck cancer for DOCETAXEL 75 mg/m² in combination with cisplatin and 5-fluorouracil
Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA System Organ classes	**Very common adverse reactions ≥ 10% of patients**	**Common adverse reactions ≥ 1 to < 10% of patients**	**Uncommon adverse reactions ≥ 0.1 to < 1% of patients**
Investigations		Weight increased	
Cardiac disorders		Myocardial ischemia (G3/4: 1.7%)	Arrhythmia (G3/4: 0.6%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 76.3%); Anemia (G3/4: 9.2%); Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia	
Nervous system disorders	Dysgeusia/Parosmia; Peripheral sensory neuropathy (G3/4: 0.6%)	Dizziness	
Eye disorders		Lacrimation increased; Conjunctivitis	
Ear and labyrinth disorders		Hearing impaired	
Gastrointestinal disorders	Nausea (G3/4: 0.6%); Stomatitis (G3/4: 4.0%); Diarrhea (G3/4: 2.9%); Vomiting (G3/4: 0.6%)	Constipation; Esophagitis/dysphagia/ odynophagia (G3/4: 0.6%); Abdominal pain; Dyspepsia; Gastrointestinal hemorrhage (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	Rash pruritic; Dry skin; Skin exfoliative (G3/4: 0.6%)	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.6%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		
Infections and infestations	Infection (G3/4: 6.3%); Neutropenic infection		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Cancer pain (G3/4: 0.6%)	
Vascular disorders		Venous disorder (G3/4: 0.6%)	
General disorders and administration site conditions	Lethargy (G3/4: 3.4%); Pyrexia (G3/4: 0.6%); Fluid retention; Edema		
Immune system disorders		Hypersensitivity (no severe)	

Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA System Organ classes	**Very common adverse reactions ≥ 10% of patients**	**Common adverse reactions ≥ 1 to < 10% of patients**	**Uncommon adverse reactions ≥ 0.1 to < 1% of patients**
Investigations	Weight decreased		Weight increased
Cardiac disorders		Arrhythmia (G3/4: 2.0%)	Myocardial ischemia
Blood and lymphatic system disorders	Neutropenia (G3/4: 83.5%); Anemia (G3/4: 12.4%); Thrombocytopenia (G3/4: 4.0%); Febrile neutropenia		
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%)		
Gastrointestinal disorders	Nausea (G3/4: 13.9%); Stomatitis (G3/4: 20.7%); Vomiting (G3/4: 8.4%); Diarrhea (G3/4: 6.8%); Esophagitis/dysphagia/ odynophagia (G3/4: 12.0%); Constipation (G3/4: 0.4%)	Dyspepsia (G3/4: 0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal hemorrhage (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%); Rash pruritic	Dry skin; Desquamation	
Musculoskeletal, connective tissue bone disorders		Myalgia (G3/4: 0.4%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Cancer pain (G3/4: 1.2%)	
Vascular disorders			Venous disorder
General disorders and administration site conditions	Lethargy (G3/4: 4.0%); Pyrexia (G3/4: 3.6%); Fluid retention (G3/4: 1.2%); Edema (G3/4: 1.2%)		
Immune system disorders			Hypersensitivity

Post-marketing experience

Cardiac disorders

Rare cases of myocardial infarction have been reported.

Blood and lymphatic system disorders

Bone marrow suppression and other hematologic adverse reactions have been reported. Disseminated intravascular coagulation (DIC), often in association with sepsis or multiorgan failure, has 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 lacrimal duct obstruction resulting in excessive tearing have been rarely reported. Cases of cystoid macular oedema (CMO) have been reported in patients treated with docetaxel.

Ear and labyrinth disorders

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

Respiratory, thoracic and mediastinal disorders

Acute respiratory distress syndrome and cases of interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure sometimes fatal 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 ischemic, colitis and neutropenic enterocolitis have been reported. Rare cases of ileus and intestinal obstruction have been reported.

Skin and subcutaneous tissue disorders

Very rare cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, 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 lymphedema have been reported with docetaxel. Cases of permanent (frequency not known) alopecia have been reported.

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

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

Vascular disorders

Venous thromboembolic events have rarely been reported.

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 edema have rarely been reported.

Immune system disorders

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

Hepatobiliary disorders

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

Renal and urinary disorders

Renal insufficiency and renal failure have been reported. In about 20% of these cases there were no risk factors for acute renal failure such as concomitant nephrotoxic medicinal products and gastrointestinal disorders.

Metabolism and nutrition disorders

Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia.

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

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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 specialized 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: L01CD02

Mechanism of action

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.

Pharmacodynamic effects

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

Efficacy and Safety

Breast cancer

DOCETAXEL in combination with doxorubicin and cyclophosphamide: adjuvant therapy

Patients with operable node-positive breast cancer (TAX 316)

Data from a multicenter, open-label, randomized trial 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+), 1,491 patients were randomized to receive either docetaxel 75 mg/m² administered 1 hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (TAC arm), or doxorubicin 50 mg/m² followed by fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m² (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.

Two interim analyses and one final analysis were performed. The first interim analysis was planned 3 years after the date when half of study enrollment was done. The second interim analysis was done after 400 DFS events had been recorded overall, which led to a median follow-up of 55 months. The final analysis was performed when all patients had reached their 10-year follow-up visit (unless they had a DFS event or were lost to follow-up before). Disease-free survival (DFS) was the primary efficacy endpoint and overall survival (OS) was the secondary efficacy endpoint.

A final analysis was performed with an actual median follow-up of 96 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 10 years was reduced in patients receiving TAC compared to those who received FAC (39% versus 45%, respectively) i.e., an absolute risk reduction by 6% (p = 0.0043). Overall survival at 10 years was also significantly increased with TAC compared to FAC (76% versus 69%, respectively) i.e., an absolute reduction of the risk of death by 7% (p = 0.002). As the benefit observed in patients with 4+ nodes was not statistically significant on DFS and OS, the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis.

Overall, the study results demonstrate a positive benefit risk ratio for TAC compared to FAC.

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	0.80	0.68-0.93	0.0043	0.74	0.61-0.90	0.0020
1-3	467	0.72	0.58-0.91	0.0047	0.62	0.46-0.82	0.0008
4+	278	0.87	0.70-1.09	0.2290	0.87	0.67-1.12	0.2746

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

Patients with operable node-negative breast cancer eligible to receive chemotherapy (GEICAM 9805)

Data from a multicenter, open-label, randomized trial support the use of docetaxel for the adjuvant treatment of patients with operable node-negative breast cancer eligible to receive chemotherapy. 1,060 patients were randomized to receive either docetaxel 75 mg/m² administered 1-hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² (539 patients in TAC arm), or doxorubicin 50 mg/m² followed by fluorouracil 500 mg/m² and cyclosphosphamide 500 mg/m² (521 patients in FAC arm), as adjuvant treatment of operable node-negative breast cancer patients with high risk of relapse according to 1998 St. Gallen criteria (tumour size > 2 cm and/or negative ER and PR and/or high histological/nuclear grade (grade 2 to 3) and/or age < 35 years)). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion; all other drugs were given intravenously on day 1 every three weeks. Primary prophylactic G-CSF was made mandatory in TAC arm after 230 patients were randomized. The incidence of Grade 4 neutropenia, febrile neutropenia and neutropenic infection was decreased in patients who received primary G-CSF prophylaxis (see section 4.8). In both arms, after the last cycle of chemotherapy, patients with ER+ and/or PgR+ tumours received tamoxifen 20 mg once a day for up to 5 years. Adjuvant radiation therapy was administered according to guidelines in place at participating institutions and was given to 57.3% of patients who received TAC and 51.2% of patients who received FAC.

One primary analysis and one updated analysis were performed. The primary analysis was done when all patients had a follow-up of greater than 5 years (median follow-up time of 77 months). The updated analysis was performed when all patients had reached their 10-year (median follow-up time of 10 years and 5 months) follow-up visit (unless they had a DFS event or were lost to follow-up previously). Disease-free survival (DFS) was the primary efficacy endpoint and Overall survival (OS) was the secondary efficacy endpoint.

At the median follow-up time of 77 months, significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. TAC-treated patients had a 32% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.68, 95% CI (0.49-0.93), p = 0.01). At the median follow-up time of 10 years and 5 months, TAC-treated patients had a 16.5% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.84, 95% CI (0.65-1.08), p = 0.1646). DFS data were not statistically significant but were still associated with a positive trend in favour of TAC.

At the median follow-up time of 77 months, overall survival (OS) was longer in the TAC arm with TAC-treated patients having a 24% reduction in the risk of death compared to FAC (hazard ratio = 0.76, 95% CI (0.46-1.26, p = 0.29). However, the distribution of OS was not significantly different between the 2 groups.

At the median follow-up time of 10 years and 5 months, TAC-treated patients had a 9% reduction in the risk of death compared to FAC-treated patients (hazard ratio = 0.91, 95% CI (0.63-1.32)).

The survival rate was 93.7% in the TAC arm and 91.4% in the FAC arm, at the 8-year follow-up timepoint, and 91.3% in the TAC arm and 89% in the FAC arm, at the 10-year follow-up timepoint.

The positive benefit risk ratio for TAC compared to FAC remained unchanged.

TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed in the primary analysis (at the median follow-up time of 77 months) (see table below):

Subset Analyses-Adjuvant Therapy in Patients with Node-negative Breast Cancer Study (Intent-to-Treat Analysis)

Patient subset	Number of patients in TAC group	Disease-Free Survival	
		Hazard ratio*	95% CI
Overall	539	0.68	0.49-0.93
Age category 1			
< 50 years	260	0.67	0.43-1.05
≥ 50 years	279	0.67	0.43-1.05
Age category 2			
< 35 years	42	0.31	0.11-0.89
≥ 35 years	497	0.73	0.52-1.01
Hormonal receptor status			
Negative	195	0.7	0.45–1.1
Positive	344	0.62	0.4–0.97
Tumour size			
≤ 2 cm	285	0.69	0.43-1.1
> 2 cm	254	0.68	0.45-1.04
Histological grade			
Grade1 (includes grade not assessed)	64	0.79	0.24-2.6
Grade 2	216	0.77	0.46-1.3
Grade 3	259	0.59	0.39-0.9
Menopausal status			
Pre-Menopausal	285	0.64	0.40-1
Post-Menopausal	254	0.72	0.47-1.12

* a hazard ratio (TAC/FAC) of less than 1 indicates that TAC is associated with a longer disease-free survival compared to FAC.

Exploratory subgroup analyses for disease-free survival for patients who meet the 2009 St. Gallen chemotherapy criteria – (ITT population) were performed and presented here below:

Subgroups	**TAC (n = 539)**	**FAC (n = 521)**	**Hazard ratio (TAC/FAC) (95% CI)**	**p-value**
Meeting relative indication for chemotherapy[a]				
No	18/214 (8.4%)	26/227 (11.5%)	0.796 (0.434-1.459)	0.4593
Yes	48/325 (14.8%)	69/294 (23.5%)	0.606 (0.42-0.877)	0.0072

TAC = docetaxel, doxorubicin and cyclophosphamide
FAC = 5-fluorouracil, doxorubicin and cyclophospamide
CI = confidence interval; ER = estrogen receptor
PR = progesterone receptor
[a] ER/PR-negative or Grade 3 or tumor size > 5 cm

The estimated hazard ratio was calculated using Cox proportional hazard model with treatment group as the factor.

DOCETAXEL as single agent

Two randomized 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 "Undesirable Effects"). 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 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 trial, AT arm showed a higher incidence of severe neutropenia (90% versus 68.6%), febrile neutropenia (33.3% versus 10%), infection (8% versus 2.4%), diarrhea (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 anemia (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 tumors overexpress HER2, and who previously had not received chemotherapy for metastatic disease. One hundred eighty six patients were randomized to receive docetaxel (100 mg/m²) 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 trial was immunohistochemistry (IHC). A minority of patients were tested using fluorescence *in situ* hybridization (FISH). In this trial, 87% of patients had disease that was IHC 3+, and 95% of patients entered had disease that was IHC 3+ and/or FISH positive. Efficacy results are summarized in 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, randomized, controlled phase III clinical trial 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 trial, 255 patients were randomised to treatment with docetaxel (75 mg/m² as a 1-hour intravenous infusion every 3 weeks) and capecitabine (1,250 mg/m² twice daily for 2 weeks followed by 1-week rest period). 256 patients were randomised to treatment with docetaxel alone (100 mg/m² 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 morphine analgesic (p < 0.01), non-morphine 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 trial, 1,218 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/m² as a 1-hour infusion immediately followed by cisplatin (Cis) 75 mg/m² over 30-60 minutes every 3 weeks, docetaxel 75 mg/m² 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/m² administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m² administered on day 1 of cycles repeated every 4 weeks.

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 Karnofsky performance status. Results on these end-points were supportive of the primary end-point 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 trial. 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	153	154	157
Pain response rate (%)	34.6	31.2	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

Due to 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 trial, 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/m² on day 1) in combination with cisplatin (C) (75 mg/m² on day 1) and 5-fluorouracil (F) (750 mg/m² per day for 5 days) or cisplatin (100 mg/m² on day 1) and 5-fluorouracil (1,000 mg/m² 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 favor of the TCF arm. Overall survival was also significantly longer (p = 0.0201) in favor 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 logrank test

Subgroup analyses across age, gender and race consistently favored 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 favor 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 (TAX 323)

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 trial (TAX 323). 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) 1,000 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 favors docetaxel + cisplatin + 5-FU
* Cox model (adjustment for Primary tumor site, T and N clinical stages and PSWHO)
** Logrank 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 favor 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 (TAX 324)

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 trial (TAX 324). 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) 1,000 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) 1,000 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 +/- 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 favors 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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with docetaxel in all subsets of the paediatric population in breast cancer, non-small cell lung cancer, prostated cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of docetaxel has been evaluated in cancer patients after administration of 20-115 mg/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 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/m² 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/m² and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

Elimination

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.

Special populations

Age and gender

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 was not altered by the age or sex of the patient.

Hepatic impairment

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: "Posology and method of administration").

Fluid retention

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.

Combination therapy

Doxorubicin

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 was not influenced by their co-administration.

Capecitabine

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.

Cisplatin

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.

Cisplatin and 5-Fluorouracil

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

Prednisone and Dexamethasone

The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients.

Prednisone

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

Citric Acid Anhydrous
Macrogol 300
Polysorbate 80
Ethanol 96%

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6: "Special precautions for disposal and other handling".

6.3 Shelf life

As packaged for sale:
Unopened: 24 months
After first opening: 28 days. Do not store above 25°C.

Shelf life after dilution:
The chemical and physical stability in Glucose 5% or Sodium chloride 0.9% (0.3 or 0.75 mg/ml, respectively, has been demonstrated for 4 h at 2-8°C (protected from light) and R.T. (20-25°C) with or w/o light protection.

From a microbiological point of view, the product should be used immediately. In-use storage times and conditions prior to use are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale:
Do not store above 25°C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3: "Shelf Life".

6.5 Nature and contents of container

Clear type I glass vial with rubber stopper and aluminum crimp cap, with or without a protective plastic overwrap
1 vial containing 20 mg/2 ml
1 vial containing 80 mg/8 ml
1 vial containing 160 mg/16 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Docetaxel solution for infusion is an oversaturated solution and therefore can crystallise/precipitate over time. The infusion solution prepared using docetaxel concentrate for solution for infusion, should be visually inspected carefully for precipitation prior to use. If the infusion solution is not clear or appears to have precipitation it has to be discarded.

From a microbiological point of view, the product should be used immediately.

Inspection prior to use

As with all parenteral drug products, Docetaxel Ebewe concentrate for solution for infusion should be inspected visually for particulate matter and discolouration, prior to use, whenever solution and container permit, solutions containing a precipitate should be discarded.

Preparation of the infusion solution

Should be diluted before use.

Infusion solutions have to be prepared with either 0.9% sodium chloride or with 5% glucose and administered as an intravenous infusion.

If the vials are stored under refrigeration, allow the required number of vials of Docetaxel Ebewe concentrate for solution for infusion to stand below 25°C until the solution has reached room temperature.

The required volume can be directly withdrawn from the vial.

More than one 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 volume containing 10 mg/ml docetaxel from the appropriate number of vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 14 ml docetaxel concentrate for solution for infusion.

The required volume of docetaxel concentrate for solution for infusion must be injected via a single injection (one shot) into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution for infusion.

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 by gentle inversion and rotation in a controlled manner and avoid foaming. Shaking or vigorous agitation has to be avoided during preparation and transportation to the patient for administration.

The prepared docetaxel infusion solution is stable for up to 4 hours and should be used within these 4 hours, including storage and the one-hour infusion time to the patient. The infusion should be aseptically administered at room temperature (below 25°C) and normal lighting conditions.

The infusion solution prepared using docetaxel concentrate for solution for infusion, should be visually inspected carefully for precipitation prior to use. If the infusion solution is not clear or appears to have precipitation it has to be discarded.

From a microbiological point of view, the product should be used immediately.

Contact of the Docetaxel Ebewe concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final Docetaxel Ebewe dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

To minimize the potential for precipitation of the infusion solution, the use of bags is recommended.

Glass bottles are not recommended for use.

pH and osmolality of reconstituted solution

0.3 mg/mL in Glucose 5%: pH ≈ 3.6; 517 mOsm/kg
0.74 mg/mL in NaCl 0.9%: pH ≈ 3.3 – 3.6; 849 mOsm/kg

Guidelines for the Safe Handling of Antineoplastic Agents:

Cytotoxic preparations should not be handled by pregnant staff. Trained personnel should dilute the drug. This should be performed in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves, masks, and clothing should be worn. Precautions should be taken to avoid the drug accidentally coming into contact with skin or mucous membranes; the affected area should be cleaned thoroughly with soap and water. If accidental contamination occurs with the eyes, they should be washed with water thoroughly and immediately.

Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.

Any unused contents should be discarded. Adequate care and precaution should be taken in the disposal of items used to dilute Docetaxel Ebewe. Any unused product or contaminated materials should be placed in a high-risk waste bag. Sharp objects (needles, syringes, vials, etc.) should be placed in a suitable rigid container. Personnel concerned with the collection and disposal of this waste should be aware of the hazard involved. Any unused product or waste material should be disposed of in accordance with standard procedures applicable to cytotoxic agents. Any excess drug solution should be flushed directly into a drain with copious amounts of water.

The medical product is for single use only.

Administration

Docetaxel Ebewe is for intravenous use only.

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG
4866 Unterach
AUSTRIA

8. IMPORTER & LICENSE HOLDER

Pharmalogic Ltd.,
P.O.B. 3838,
Petah-Tikva 4951623
Reg Number:
146-55-33269-00

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