Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Docirena 20 mg/1 ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 20 mg docetaxel anhydrous.
One vial of 1 ml of concentrate contains 20 mg of docetaxel.

Excipients wih known effect:
Each vial of 1 ml of concentrate contains 0.57 ml of ethanol 96% (0.46 g).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear viscous, colourless to brownish-yellow sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Breast cancer
Docirena in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

- operable node- positive breast cancer.
- operable node- negative breast cancer.

For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer (see section 5.1).
Docirena 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.

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

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

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

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

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

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

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

Head and neck cancer
Docirena in combination with cisplatin and 5−fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

4.2 Posology and method of administration

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

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

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

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

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

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

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

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

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

Head and neck cancer
Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylactic G−CSF may be used to mitigate the risk of haematological toxicities. All patients on the docetaxel-containing arm of the 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 organpreservation) squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75 mg/m^2 as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m^2 administered as a 30-minute to 3-hour infusion, followed by 5-fluorouracil 1000 mg/m^2/day as a continuous infusion from day 1 to day 4. This regimen is administered every 3 weeks for 3 cycles. Following chemotherapy, patients should receive chemoradiotherapy.

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

Dose adjustments during treatment

General
Docetaxel should be administered when the neutrophil count is ≥ 1,500 cells/mm^3.
In patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/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 and 4.8). 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 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the docetaxel dose in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin 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 Grade 2 toxicity, which persists at the time of the next docetaxel/capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100% of the original dose.
- For patients developing the second appearance of 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 and then resume treatment with docetaxel 55 mg/m².
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose.

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

In combination with cisplatin and 5-fluorouracil

If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G−CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist (see section 4.4).
Recommended dose modifications for toxicities in patients treated with docetaxel in combination with cisplatin and 5−fluorouracil (5−FU):

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

For cisplatin and 5−fluorouracil dose adjustments, see the corresponding summary of product characteristics.

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

Special populations

Patients with hepatic impairment
Based on pharmacokinetic data with docetaxel at 100 mg/m² as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2 (see sections 4.4 and 5.2). For those patients with serum bilirubin > ULN and/or ALT and AST > 3.5 times the ULN associated with alkaline phosphatase > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.
In combination with cisplatin and 5−fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical study excluded patients with ALT and/or AST > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin > 1 x ULN; for these patients, no dose-reductions can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination in the other indications.

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.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Patients with baseline neutrophil count of < 1,500 cells/mm^3.

Patients with severe liver impairment (see sections 4.2 and 4.4).

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

4.4 Special warnings and precautions for use

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

Haematology
Neutropenia is the most frequent adverse reaction of docetaxel. Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre−treated patients. Frequent monitoring of complete blood counts should be

conducted on all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level ≥ 1,500 cells/mm3 (see section 4.2).

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

In patients treated with docetaxel in combination with cisplatin and 5−fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G−CSF. Patients treated with TCF should receive prophylactic G−CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TCF should be closely monitored (see sections 4.2 and 4.8).

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 and 4.8).

Hypersensitivity reactions
Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

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

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

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

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

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

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

Additional cautions for use in adjuvant treatment of breast cancer
Complicated neutropenia
For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G−CSF and dose reduction should be considered (see section 4.2).

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

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

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

Patients with 4+ nodes
As the benefit observed in patient 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).

Elderly patients
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, diarrhoea, anorexia, and peripheral oedema occurred at rates ≥ 10% higher in patients who were 75 years of age or greater versus less than 65 years.

Among the 300 (221 patients in the phase III part of the study and 79 patients in the phase II part) patients treated with docetaxel in combination with cisplatin and 5−fluorouracil in the gastric cancer study, 74 were 65 years of age or older and 4 patients were 75 years of age or older. The incidence of serious adverse events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis,

neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients.
Elderly patients treated with TCF should be closely monitored.

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Excipients
This medicinal product contains approximately 55 vol % ethanol (alcohol), i.e. up to 0.459 g (0.57 ml) ethanol 96 % per vial, equivalent to 12 ml of beer or 5 ml wine per vial.

Harmful for those 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 epilepsy.

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

The amount of alcohol in this medicinal product may impair the patients 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 metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450−3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

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

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

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

Clinical cases consistent with an increase in docetaxel toxicity were reported when it was combined with ritonavir. The mechanism behind this interaction is a CYP3A4 inhibition, the main isoenzyme involved in docetaxel metabolism by ritonavir. Based on extrapolation from a pharmacokinetic study with ketoconazole in 7 patients, consider a 50% docetaxel dose reduction if patients require co-administration of a strong CYP3A4 inhibitor such as azole antifungals, ritonavir and some macrolides (clarithromycin, telithromycin).

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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile for all indiations

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

- 1312 and 121 patients who received 100 mg/m² and 75 mg/m² of docetaxel as a single agent respectively.
- 258 patients who received docetaxel in combination with doxorubicin.
- 406 patients who received docetaxel in combination with cisplatin.
- 92 patients treated with docetaxel in combination with trastuzumab.
- 255 patients who received docetaxel in combination with capecitabine.
- 332 patients who received docetaxel in combination with prednisone or prednisolone (clinically important treatment related adverse events are presented).
- 1276 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). the COSTART and the MedDRA terms. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most commonly reported adverse reactions of docetaxel alone are: neutropenia (which was reversible and not cumulative; the median day to nadir was 7 days and the median duration of severe neutropenia (< 500 cells/mm^3) was 7 days), anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of

docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

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

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

The following adverse reactions are frequently observed with docetaxel:

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

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

Skin and subcutaneous tissue disorders
Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the arms, face or thorax, and frequently associated with pruritus. Eruptions generally occurred within one week after the docetaxel infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely lead to interruption or discontinuation of docetaxel treatment were reported (see sections 4.2 and 4.4). Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

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

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Blood and lymphatic system disorders	Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%); Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	
Immune system disorders	Hypersensitivity (G3/4: 5.3%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%);		

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

Tabulated list of adverse reactions in breast cancer for ***docetaxel 100 mg/m² single agent***

Description of selected adverse reactions in breast cancer for docetaxel100 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/m² as single agent. The events were spontaneously reversible within 3 months.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

The median cumulative dose to treatment discontinuation was more than 1,000 mg/m^2 and the median time to fluid retention reversibility was 16.4 weeks (range 0 to 42 weeks). The onset of moderate and severe retention is delayed

(median cumulative dose: 818.9 mg/m^2) in patients with premedication compared with patients without premedication (median cumulative dose: 489.7 mg/m^2); however, it has been reported in some patients during the early courses of therapy.

Tabulated list of adverse reactions in breast cancer for ***docetaxel 75mg/m² single agent:***

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

Tabulated list of adverse reactions in breast cancer for ***docetaxel 75mg/m² in combination with doxorubicin:***

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 7.8%)		
Blood and lymphatic system disorders	Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4:0.8 %)		
Immune system disorders		Hypersensitivity (G3/4: 1.2 %)	
Metabolism and nutrition disorders		Anorexia	

Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Cardiac disorders		Cardiac failure; Arrhythmia (no severe)	
Vascular disorders			Hypotension
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhoea (G3/4: 6.2%); Vomiting (G3/4: 5%); Constipation		
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe 0.4%); Skin reaction (no severe)		
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions	Asthenia (severe 8.1%); Fluid retention (severe 1.2%); Pain	Infusion site reaction	
Investigations		G3/4 Blood bilirubin increased (< 2.5 %); G3/4 Blood alkaline phosphatase increased (< 2.5 %)	G3/4 AST increased (<1 %); G3/4 ALT increased (< 1 %)

Tabulated list of adverse reactions in breast cancer for ***docetaxel 75 mg/m² in combination with cisplatin***

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 5.7%)		
Blood and lymphatic system disorders	Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%); Peripheral motor neuropathy (G3/4: 2%)		
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Vascular disorders		Hypotension (G3/4: 0.7%)	
Gastrointestinal disorders	Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%)	Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe:		

	0.7%); Skin reaction (G3/4: 0.2%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe: 0.5%)		
General disorders and administration site conditions	Asthenia (severe: 9.9%); Fluid retention (severe: 0.7%); Fever (G3/4: 1.2%)	Infusion site reaction; Pain	
Investigations		G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased (1.3%)	G3/4 AST increased (0.5%); G3/4 Blood alkaline phosphatase increased (0.3%)

Tabulated list of adverse reactions in breast cancer for ***docetaxel 100 mg/m² in combination with trastuzumab***

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

Description of selected adverse reactions in breast cancer for docetaxel100 mg/m^2 in combination with trastuzumab

Blood and lymphatic system disorders
Very common: Haematological toxicity was increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 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).

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.

Tabulated list of adverse reactions in breast cancer for ***docetaxel 75mg/m² in combination with capecitabine:***

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations		Oral candidiasis (G3/4: <1%)
Blood and lymphatic system disorders	Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%); Decreased appetite	Dehydration (G3/4: 2%);
Nervous system disorders	Dysgeusia (G3/4: <1%); 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%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4: 2%); Dyspepsia	Abdominal pain upper; Dry mouth
Skin and subcutaneous tissue disorders	Hand-foot syndrome (G3/4: 24%) Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%)	Dermatitis; Rash erythematous (G3/4: <1%); Nail discolouration; Onycholysis (G3/4: 1%)
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%);
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4: 5%); Oedema peripheral (G3/4: 1%);	Lethargy; Pain
Investigations		Weight decreased; G3/4 Blood bilirubin increased (9%)

Tabulated list of adverse reactions in breast cancer for ***docetaxel 75 mg/m² in combination with prednisone or prednisolone***

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Infection (G3/4: 3.3%)	
Blood and lymphatic system disorders	Neutropenia (G3/4: 32%); Anaemia (G3/4: 4.9%)	Thrombocytopenia (G3/4: 0.6%); Febrile neutropenia
Immune system disorders		Hypersensitivity (G3/4: 0.6%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	

Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G3/4: 0.6%)
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%); Dyspnoea (G3/4: 0.6%); Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (no severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective bone disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe: 0.6%)	

Tabulated list of adverse reactions in breast cancer 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**	**Common adverse reactions**	**Uncommon adverse reactions**
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: 5.0%); Stomatitis (G3/4: 6.0%); 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 (G3/4: <0.1%); 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: 10.0%); 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/m² 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 (TAX316).

Cardiac disorders

In study TAX316, 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

Skin and subcutaneous tissue disorders

In study TAX316, alopecia persisting into the follow-up period after the end of chemotherapy was reported in 687 TAC patients and 645 FAC patients.

At the end of the follow-up period, alopecia was observed to be ongoing in 29 TAC patients (4.2%) and 16 FAC patients (2.4%).

Reproductive system and breast disorders

Amenorrhoea was observed to be ongoing during follow-up in 121 patients out of the 202 patientswith amenorrhoea at the end of the chemotherapy in study TAX316.

General disorders and administration site conditions

In study TAX316, 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 with

lymphoedema at the end of the chemotherapy

Acute leukaemia / Myelodysplastic syndrome.

At a median follow-up time of 77 months, acute leukaemia occurred in 1 of 532 (0.2%) patients who received docetaxel, doxorubicin, and cyclophosphamide in the GEICAM 9805 study. No cases were reported in patients who

received fluorouracil, doxorubicin and cyclophosphamide. No patient was diagnosed with myelodysplastic syndrome in either treatment groups.

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.

Acute leukaemia / Myelodysplastic syndrome.

After 10 years of follow up in study TAX316, 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.

At a median follow-up time of 77 months, acute leukaemia occurred in 1 of 532 (0.2%) patients who received docetaxel, doxorubicin, and cyclophosphamide in the GEICAM 9805 study. No cases were reported in patients who received fluorouracil, doxorubicin and cyclophosphamide. No patient was diagnosed with myelodysplastic syndrome in either treatment groups.

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 breast cancer for d***ocetaxel 75 mg/m² in combination with cisplatin and 5 –fluorouracil***

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Neutropenic infection; Infection (G3/4: 11.7%)	
Blood and lymphatic system disorders	Anaemia (G3/4: 20.9%); Neutropenia (G3/4: 83.2%); Thrombocytopenia (G3/4: 8.8%); Febrile neutropenia	
Immune system disorders	Hypersensitivity (G3/4: 1.7%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%)	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 8.7%)	Dizziness (G3/4: 2.3%); Peripheral motor neuropathy (G3/4: 1.3%)

Eye disorders		Lacrimation increased (G3/4: 0%)
Ear and labyrinth disorders		Hearing impaired (G3/4: 0%)
Cardiac disorders		Arrhythmia (G3/4: 1.0%)
Gastrointestinal disorders	Diarrhoea (G3/4: 19.7%); Nausea (G3/4: 16%); Stomatitis (G3/4: 23.7%); Vomiting (G3/4: 14.3%)	Constipation (G3/4: 1.0%); Gastrointestinal pain (G3/4: 1.0%); Oesophagitis/dysphagia/odynophagia (G3/4: 0.7%)
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%)	Rash pruritus (G3/4: 0.7%); Nail disorders (G3/4: 0.7%); Skin exfoliation (G3/4: 0%)
General disorders and administration site conditions	Lethargy (G3/4: 19.0%); Fever (G3/4: 2.3%); Fluid retention (severe/life-threatening: 1%)	

Description of selected adverse reactions in gastric adenocarcinoma cancer for docetaxel 75 mg/m^2 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).

Tabulated list of adverse reactions in breast 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**	**Common adverse reactions**	**Uncommon adverse reactions**
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%)	
Blood and lymphatic system disorders	Neutropenia (G3/4: 76.3%); Anaemia (G3/4: 9.2%); Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia	
Immune system disorders		Hypersensitivity (no severe)	
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		
Nervous system disorders	Dysgeusia/Parosmia; Peripheral sensory neuropathy (G3/4: 0.6%)	Dizziness	
Eye disorders		Lacrimation increased; Conjunctivitis	
Ear and labyrinth disorders		Hearing impaired	
Cardiac disorders		Myocardial ischemia (G3/4:1.7%)	Arrhythmia (G3/4: 0.6%)
Vascular disorders		Venous disorder (G3/4:	

		0.6%)	
Gastrointestinal disorders	Nausea (G3/4: 0.6%); Stomatitis (G3/4: 4.0%); Diarrhoea (G3/4: 2.9%); Vomiting (G3/4: 0.6%)	Constipation; Esophagitis/dysphagia/ odynophagia (G3/4: 0.6%); Abdominal pain; Dyspepsia; Gastrointestinal haemorrhage (G3/4: 0.6%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	Rash pruritic; Dry skin; Skin exfoliative (G3/4: 0.6%)	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.6%)	
General disorders and administration site conditions	Lethargy (G3/4: 3.4%); Pyrexia (G3/4: 0.6%); Fluid retention; Oedema		
Investigations		Weight increased	

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Cancer pain (G3/4: 1.2%)	
Blood and lymphatic system disorders	Neutropenia (G3/4: 83.5%); Anaemia (G3/4: 12.4%); Thrombocytopenia (G3/4: 4.0%); Febrile neutropenia		
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
Nervous system disorders	Dysgeusia/Parosmia (G3/4: 0.4%); Peripheral sensory neuropathy (G3/4: 1.2%)	Dizziness (G3/4: 2.0%); Peripheral motor neuropathy (G3/4: 0.4%)	
Eye disorders		Lacrimation increased	Conjunctivitis
Ear and labyrinth disorders	Hearing impaired (G3/4: 1.2%)		
Cardiac disorders		Arrhythmia (G3/4: 2.0%)	Ischemia myocardial
Vascular disorders			Venous disorder
Gastrointestinal disorders	Nausea (G3/4: 13.9%); Stomatitis (G3/4: 20.7%); Vomiting (G3/4: 8.4%); Diarrhoea (G3/4: 6.8%); Esophagitis/dysphagia/ odynophagia (G3/4:	Dyspepsia (G3/4: 0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4: 0.4%)	

	12.0%); Constipation (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%)	
General disorders and administration site conditions	Lethargy (G3/4: 4.0%); Pyrexia (G3/4: 3.6%); Fluid retention (G3/4: 1.2%); Oedema (G3/4: 1.2%)		
Investigations	Weight decreased		Weight increased

Post-marketing experience

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

Cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported in association with docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.

Blood and lymphatic system disorders

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

Immune system disorders

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

Nervous system disorders

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

Eye disorders

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

Ear and labyrinth disorders

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

Cardiac disorders

Rare cases of myocardial infarction have been reported.

Vascular disorders

Venous thromboembolic events have rarely been reported.

Respiratory, thoracic and mediastinal disorders

Acute respiratory distress syndrome and cases of interstitial pneumonia and pulmonary fibrosis 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 ischaemic, colitis and neutropenic enterocolitis have been reported. Rare cases of ileus and intestinal obstruction have been reported.

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders
Very rare cases of cutaneous lupus 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 lymphoedema have been reported with docetaxel. Cases of persisting alopecia 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.

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

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Taxanes, ATC Code: 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.

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

Clinical 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 study support the use of docetaxel for the adjuvant treatment of patients

with operable node-positive breast cancer and KPS ≥ 80%, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either docetaxel 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 (TAC arm), or doxorubicin 50 mg/m^2 followed by fluorouracil 500 mg/m^2 and cyclosphosphamide 500 mg/m^2 (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion, all other medicinal products were given as intravenous bolus on day one. G−CSF was administered as secondary prophylaxis to patients who experienced complicated neutropenia (febrile neutropenia, prolonged neutropenia, or infection). Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20 mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

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.
An interim
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 whoreceived 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

<u>Patients with operable node-negative breast cancer eligible to receive chemotherapy</u> (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.
1060 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. Docirena was administered as a 1-hour infusion, all other medicinal products were given intraveinously 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.

Median duration of follow-up was 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). Overall survival (OS) was also 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.

TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed (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 tumour size >5 cm
The estimated hazard ratio was using Cox proportional hazard model with treatment group as the factor.

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

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

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

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

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

More grade 3/4 adverse events were observed for docetaxel monotherapy (55.4%) compared to paclitaxel (23.0%).

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

- Time to progression (TTP) was significantly longer in the AT arm versus AC arm, p = 0.0138. The median TTP was 37.3 weeks (95% CI: 33.4 − 42.1) in AT arm and 31.9 weeks (95% CI: 27.4 − 36.0) in AC arm.
- Overall response rate (ORR) was significantly higher in the AT arm versus AC arm, p = 0.009. The ORR was 59.3% (95% CI: 52.8 − 65.9) in AT arm versus 46.5% (95% CI: 39.8 − 53.2) in AC arm.

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

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

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

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

Docetaxel in combination with capecitabine
Data from one multicenter, randomised, controlled phase III clinical study support the use of docetaxel in combination with capecitabine for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic

chemotherapy, including an anthracycline. In this study, 255 patients were randomised to treatment with docetaxel (75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks) and capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by 1−week rest period). 256 patients were randomised to treatment with docetaxel alone (100 mg/m^2 as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel + capecitabine combination arm ($p = 0.0126$). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone). The overall objective response rates in the all−randomised population (investigator assessment) were 41.6% (docetaxel + capecitabine) vs. 29.7% (docetaxel alone); $p = 0.0058$. Time to progressive disease was superior in the docetaxel + capecitabine combination arm ($p < 0.0001$). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone).

Non-small cell lung cancer

Patients previously treated with chemotherapy with or without radiotherapy
In a phase III study, in previously treated patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 75 mg/m² compared to Best Supportive Care. The 1−year survival rate was also significantly longer in docetaxel (40%) versus BSC (16%).
There was less use of morphinic analgesic ($p < 0.01$), non-morphinic analgesics ($p < 0.01$), other disease-related medicinal products ($p = 0.06$) and radiotherapy ($p < 0.01$) in patients treated with docetaxel at 75 mg/m² compared to those with BSC.
The overall response rate was 6.8% in the evaluable patients, and the median duration of response was 26.1 weeks.

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

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

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

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

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

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

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Prostate cancer

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

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

All 3 regimens were administered in combination with prednisone or prednisolone 5 mg twice daily, continuously. Patients who received docetaxel every three weeks demonstrated significantly longer overall survival compared to those treated with 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
Tumour response rate (%)	12.1	8.2	6.6
95% CI	(7.2-18.6)	(4.2-14.2)	(3.0-12.1)
p-value*	0.1112	0.5853	--

†Stratified log rank test

*Threshold for statistical significance = 0.0175

**PSA: Prostate-Specific Antigen

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

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

Gastric adenocarcinoma

A multicenter, open-label, randomized study was conducted to evaluate the safety and efficacy of docetaxel for the

treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for metastatic disease. A total of 445 patients with KPS > 70 were treated with either docetaxel (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and 5-fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and 5−fluorouracil (1000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p = 0.0004) in 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

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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)	9.2 (8.38-10.58)	8.6 (7.16-9.46)
2-year estimate (%)	18.4	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 (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the

head and neck (SCCHN) was evaluated in a phase III, multicenter, open-label, randomized study (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO perfomance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m^2 followed by cisplatin (P) 75 mg/m^2 followed by 5−fluorouracil (F) 750 mg/m^2 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/m^2 followed by 5−fluorouracil (F) 1000 mg/m^2 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 tumour 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 (TAX324)

The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a randomized, multicenter open-label, phase III study (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two arms. The study population comprised patients with technically unresectable disease, patients with low probability of surgical cure and patients aiming at organ preservation. The efficacy and safety evaluation solely addressed survival endpoints and the success of organ preservation was not formally addressed. Patients on the docetaxel arm received docetaxel (T) 75 mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m² administered as a 30−minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of 5−fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100 mg/m² as a 30−minute to three−hour intravenous infusion on day 1 followed by the continuous intravenous infusion of 5−fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).
Patients in both treatment arms were to receive 7 weeks of CRT following induction chemotherapy with a minimum interval of 3 weeks and no later than 8 weeks after start of the last cycle (day 22 to day 56 of last cycle). During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one−hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks, for a total dose of 70−72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT. All patients on the docetaxel-containing arm of the study received prophylactic antibiotics. The primary efficacy endpoint in this study, overall survival (OS) was significantly longer (log-rank test, p = 0.0058) with the docetaxel-containing regimen compared to PF (median OS: 70.6 versus 30.1 months respectively), with a 30% risk reduction in mortality compared to PF (hazard ratio (HR) = 0.70, 95% confidence interval (CI) = 0.54−0.90) with an overall median follow up time of 41.9 months. The secondary endpoint, PFS, demonstrated a 29% risk reduction of progression or death and a 22 month improvement in median PFS (35.5 months for TPF and 13.1 for PF). This was also statistically significant with an HR of 0.71; 95% CI 0.56-0.90; log-rank test p = 0.004. Efficacy results are presented in the table below:

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

Endpoint	**Docetaxel + Cis + 5−FU** **n = 255**	**Cis + 5−FU** **n = 246**
Median overall survival (months) (95% CI)	70.6 (49.0-NA)	30.1 (20.9-51.5)

Hazard ratio: (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	
Median PFS (months) (95% CI)	35.5 (19.3-NA)	13.1 (10.6 - 20.2)
Hazard ratio: (95% CI) **p-value	0.71 (0.56 - 0.90) 0.004	
Best overall response (CR + PR) to chemotherapy (%) (95% CI)	71.8 (65.8-77.2)	64.2 (57.9-70.2)
***p-value	0.070	
Best overall response (CR + PR) to study treatment [chemotherapy +/- 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 popultaion
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 have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the a, b and g 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.

Distribution
Following the administration of a 100 mg/m^2 dose given as a one−hour infusion a mean peak plasma level of 3.7 µg/ml was obtained with a corresponding AUC of 4.6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m^2 and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

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 population
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

were 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 ³ 1.5 times the ULN associated with alkaline phosphatase ³ 2.5 times the ULN), total clearance was lowered by 27% on average (see section 4.2).

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 were 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 (Cmax 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

Polysorbate 80

Ethanol 96%
Citric acid monohydrate

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial 2 years

After opening of the vial
Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added to the infusion bag
From microbiological point of view, reconstitution/dilution must take place in controlled and aseptic conditions and the medicinal product should be used immediately. If not used immediately, in−use storage times and conditions are the responsibility of the user.

Once added as recommended into the infusion bag (PP) or infusion bottle (PE), the docetaxel infusion solution, if stored below 25°C, is stable for 8 hours in infusion bottle or for 6 hours in infusion bag. It should be used within 6-8 hours (including the one hour infusion IV administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 to 8°C.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Store in the original package in order to protect from light.

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

6.5 Nature and contents of container

2 ml colourless type-I glass vial, closed with a 13 mm grey chlorobutyl rubber stopper and a flip-off seal consisting of an aluminium shell and a red plastic flip-off button. The rubber stopper is coated with a Teflon® barrier film.

Each box contains one vial with 1 ml fill volume

6.6 Special precautions for disposal and other handling

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

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

Preparation for the intravenous administration

Preparation of the infusion solution
DO NOT use other docetaxel medicinal products consisting of 2 vials (concentrate and solvent) with this medicinal product (Docirena 20 mg/1 ml concentrate for solution for infusion, which contains only 1 vial).

Docirena 20 mg/1 ml concentrate for solution for infusion requires NO prior dilution with a solvent and is ready to add to the infusion solution.

Each vial is of single use and should be used immediately.

Allow the required number of boxes of Docirena concentrate for solution for infusion to stand below 25°C for 5 minutes before use.
More than one vial of Docirena concentrate for solution for infusion may be necessary to obtain the required dose for the patient. Aseptically withdraw the required amount of Docirena concentrate for solution for infusion using a calibrated syringe.

In Docirena 20 mg /1 ml vial the concentration of docetaxel is 20 mg/ml.
The required volume of Docirena 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 sodium chloride 9 mg/ml (0.9%) solution for infusion.

If a dose greater than 190 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

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

The infusion bag solution should be used within 8 hours below 25°C including the one hour infusion to the patient.
As with all parenteral products, Docirena infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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