ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Docetaxel Teva Pharma 20 mg concentrate and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial of Docetaxel Teva Pharma concentrate contains 20 mg docetaxel (anhydrous). Each ml of concentrate contains 27.73 mg docetaxel.

Excipients with known effect:
Each vial of concentrate contains 25.1% (w/w) anhydrous ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and solvent for solution for infusion.
The concentrate is a clear viscous, yellow to brown-yellow solution.
The solvent is a colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Docetaxel Teva Pharma 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.

Non-small cell lung cancer

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

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

Prostate cancer

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

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 and non-small cell lung cancer, 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
For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m^2 in monotherapy.

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).

Dose adjustments during treatment

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

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 characeteristics.

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.

Paediatric population
The safety and efficacy of Docetaxel Teva Pharma 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 Teva Pharma in the paediatric population in the indications breast cancer, non-small cell lung cancer and prostate cancer.

Older People

Based on a population pharmacokinetic analysis, there are no special instructions for use in older people.

4.3 Contraindications

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

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

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

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

4.4 Special warnings and precautions for use

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

Haematology

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

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

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

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.

Respiratory disorders

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

Patients with liver impairment

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

Patients with renal impairment

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

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.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatment initiated (see section 4.8).

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).

Older people

There are limited data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide.

Of the 333 patients treated with docetaxel every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the incidence of related nail changes occurred at a rate ≥ 10% higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, 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 older people compared to younger patients.
The incidence of the following adverse events (all grades): lethargy, stomatitis, neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients.

Older people treated with TCF should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as cyclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

Docetaxel is highly protein bound (>95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicinal products has not been investigated formally, *in vitro* interactions with tightly protein-bound drugs 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 coadministration. 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-administrtion of a stron 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.

Contracteption in males and females

An effective method of contraception should be used during treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile for all indications

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

- 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) and 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 the available data).

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

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

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

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

The following adverse reactions are frequently observed with docetaxel:

Immune system disorders

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

Nervous system disorders

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

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

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

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

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Blood and 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		

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

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

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

Nervous system disorders
Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 100 mg/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 75 mg/m² single agent

MedDRA system srgan classes	Very common adverse reactions	Common adverse reactions
Infections and infestations	Infections (G3/4: 5%)	
Blood and 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 75 mg/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 lit 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%);	Constipation	

	Stomatitis (G3/4: 2%)		
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 Docetaxel 100 mg/m^2 in combination with trastuzumab

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

Blood and lymphatic system disorders
Very common: 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).

Tabulated list of adverse reactions in breast cancer for Docetaxel 75 mg/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%); Paresthesia (G3/4: <1%)	Dizziness; Headache (G3/4: <1%); Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%)	Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%)
Gastrointestinal disorders	Stomatitis (G3/4: 18%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4: 2%); Dyspepsia	Abdominal pain upper; Dry mouth
Skin and subcutaneous tissue disorders	Hand-foot syndrome (G3/4: 24%); Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%)	Dermatitis; Rash erythematous (G3/4: <1%); Nail discolouration; Onycholysis (G3/4: 1%)
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%)
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4: 5%); Oedema peripheral (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 tissue disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)	

Tabulated list of 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 - 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%)		

MedDRA system organ classes	Very common adverse reactions	Common adverse reactions	Uncommon adverse reactions
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/m^2 in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316 and node-negative (GEICAM 9805) breast cancer

Nervous system disorders

Peripheral sensory neuropathy was observed to be ongoing during follow-up in 10 patients out of the 84 patients with peripheral sensory neuropathy at the end of the chemotherapy in the node positive breast cancer study (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 patients with 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.
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 gastric adenocarcinoma cancer for Docetaxel 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 head and neck cancer for Docetaxel 75 mg/m² in combination with cisplatin and 5-fluorouracil

- Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA system organ classes	Very common adverse reactions	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: 12.0%); Constipation (G3/4: 0.4%)	Dyspepsia (G3/4: 0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%); Rash pruritic;	Dry skin; Desquamation	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.4%)	
General disorders and administration site conditions	Lethargy (G3/4: 4.0%); Pyrexia (G3/4: 3.6%); Fluid retention (G3/4: 1.2%); Oedema (G3/4: 1.2%)		
Investigations	Weight decreased		Weight increased

Post-marketing experience

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 lachrymal duct obstruction resulting in excessive tearing have been rarely reported. Cases of cystoid macular oedema (CMO) have been reported in patients treated with docetaxel

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

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/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure sometimes fatal have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

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

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD 02

Mechanism of action

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

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

Pharmacodynamic effects

Docetaxel was found to be cytotoxic *in vitro* against various murine and human 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
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%).

Non-small cell lung cancer

Patients previously treated with chemotherapy with or without radiotherapy

In a phase III study, in previously treated patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 75 mg/m² compared to Best Supportive Care. The 1-year survival rate was also significantly longer in docetaxel (40%) versus BSC (16%). There was less use of morphinic analgesic (p<0.01), non-morphinic analgesics (p<0.01), other disease related medications (p=0.06) and radiotherapy (p<0.01) in patients treated with docetaxel at 75 mg/m² compared to those with BSC.
The overall response rate was 6.8% in the evaluable patients, and the median duration of response was 26.1 weeks.

Docetaxel in combination with platinum agents in chemotherapy-naïve patients

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

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

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

			[95% CI: 0.7; 13.5]

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

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

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

Prostate cancer

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

- Docetaxel 75 mg/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 (7.2-18.6)	8.2 (4.2-14.2)	6.6 (3.0-12.1)
95% CI	0.1112	0.5853	--
*p-value**			

†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.

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 α, β and γ phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

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 populations

Age and gender
A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from Phase I studies. The pharmacokinetics of docetaxel 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 ≥1.5 times the ULN associated with alkaline phosphatase ≥2.5 times the ULN), total clearance was lowered by 27% on average (see section 4.2).

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 coadministration.

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

Cisplatin

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

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

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

Prednisone
No effect of prednisone on the pharmacokinetics of docetaxel was observed.

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate
Polysorbate 80
Ethanol, anhydrous

Solvent
Water for injections.

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

- 18 months.
- Premix solution: Chemical and physical in-use stability has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are

the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage and other handling

Do not store above 25°C .
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton contains:

- One vial of concentrate and,
- One vial of solvent

- Docetaxel Teva Pharma 20 mg vial
  6 ml clear glass Type I vial with a bromobutyl rubber stopper and a flip-off cap.

  This vial contains 0.72 ml of a 27.73 mg/ml solution of docetaxel in polysorbate 80 (fill volume: 24.4 mg/0.88 ml). This fill volume has been established during the development of docetaxel to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for docetaxel vial, there is a minimal extractable premix volume of 2 ml containing 10 mg/ml docetaxel which corresponds to the labelled amount of 20 mg per vial.

  Solvent for Docetaxel Teva Pharma 20 mg vial
  6 ml clear glass Type I vial with a bromobutyl rubber stopper and a flip-off cap.

  Solvent vial contains 1.28 ml of water for injections (fill volume: 1.71 ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel Teva Pharma 20 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml docetaxel.

6.6 Special precautions for disposal and other handling

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

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

Preparation for the intravenous administration

a) Preparation of the Docetaxel Teva Pharma premix solution (10 mg docetaxel/ml)

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

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel Teva Pharma vial by partially inverting the vial.

Inject the entire contents of the syringe into the corresponding Docetaxel Teva Pharma vial.

Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.

Allow the premix vial to stand for 5 minutes at room temperature (below 25°C) and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).

The premix solution contains 10 mg/ml docetaxel and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C).

b) *Preparation of the infusion solution*

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

Inject the required premix volume into a non-PVC 250 ml infusion bag containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion.

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

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

The Docetaxel Teva Pharma infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature (below 25°C) and normal lighting conditions.

As with all parenteral products, Docetaxel Teva Pharma premix solution and 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

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/10/662/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st January 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Docetaxel Teva Pharma 80 mg concentrate and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose vial of Docetaxel Teva Pharma concentrate contains 80 mg docetaxel (anhydrous). Each ml of concentrate contains 27.73 mg docetaxel.

Excipients with known effect:
Each vial of concentrate contains 25.1% (w/w) anhydrous ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate and solvent for solution for infusion.
The concentrate is a clear viscous, yellow to brown-yellow solution.
The solvent is a colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Docetaxel Teva Pharma 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.

Non-small cell lung cancer

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

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

Prostate cancer

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

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 and non-small cell lung cancer, 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
For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m^2 in monotherapy.

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).

Dose adjustments during treatment

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

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 characeteristics.

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.

Paediatric population
The safety and efficacy of Docetaxel Teva Pharma 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 Teva Pharma in the paediatric population in the indications breast cancer, non-small cell lung cancer and prostate cancer.

Older people

Based on a population pharmacokinetic analysis, there are no special instructions for use in older people.

4.3 Contraindications

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

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

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

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

4.4 Special warnings and precautions for use

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

Haematology

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

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

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

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.

Respiratory disorders

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

Patients with liver impairment

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

Patients with renal impairment

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

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.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examiniation. In case CMO is diagnosed, docetaxel treatment should be discontinued and appropriate treatement initiated (see section 4.8).

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).

Older people

There are limited data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide.

Of the 333 patients treated with docetaxel every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the incidence of related nail changes occurred at a rate ≥ 10% higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, 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 older people compared to younger patients.
The incidence of the following adverse events (all grades): lethargy, stomatitis, neutropenic infection occurred at rates ≥ 10% higher in patients who were 65 years of age or older compared to younger patients.

Older people treated with TCF should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as cyclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction.

Docetaxel is highly protein bound (>95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicinal products has not been investigated formally, *in vitro* interactions with tightly protein-bound drugs 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 coadministration. 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.

Clincal 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.

Contraception in males and females

An effective method of contraception should be used during treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile for all indications

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

- 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) and the COSTART and the MedRA terms. Frequencies are defined as: very common (≥1/10), common (≥1/100 to < 1/10); uncommon (≥1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

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

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

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

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

The following adverse reactions are frequently observed with docetaxel:

Immune system disorders

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

Nervous system disorders

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

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

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

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

MedDRA system organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Blood and 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%);		

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

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

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

Nervous system disorders
Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 100 mg/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 75 mg/m² single agent

MedDRA system organ classes	Very common adverse reactions	Common adverse reactions
Infections and infestations	Infections (G3/4: 5%)	
Blood and 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 75 mg/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%);	Constipation	

	Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%)		
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 Docetaxel 100 mg/m^2 in combination with trastuzumab

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

Blood and lymphatic system disorders
Very common: 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).

Tabulated list of adverse reactions in breast cancer for Docetaxel 75 mg/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%); Paresthesia (G3/4: <1%)	Dizziness; Headache (G3/4: <1%); Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%)	Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%)
Gastrointestinal disorders	Stomatitis (G3/4: 18%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4: 2%); Dyspepsia	Abdominal pain upper; Dry mouth
Skin and subcutaneous tissue disorders	Hand-foot syndrome (G3/4: 24%); Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%)	Dermatitis; Rash erythematous (G3/4: <1%); Nail discolouration; Onycholysis (G3/4: 1%)
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%)
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4: 5%); Oedema peripheral (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		Hypersensivity (G3/4: 0.6%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G 3/4; 0.6%)
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%); Dyspnoea (G3/4: 0.6%); Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (no severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)	

Tabulated list of adverse reactions in breast cancer 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 - 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%)	

MedDRA system organ classes	Very common adverse reactions	Common adverse reactions	Uncommon adverse reactions
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/m^2 in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316) and node-negative (GEICAM 9805) breast cancer

Nervous system disorders
Peripheral sensory neuropathy was observed to be ongoing during follow-up in 10 patients out of the 84 patients with peripheral sensory neuropathy at the end of the chemotherapy in the node positive breast cancer study (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 patients with 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.
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 gastric adenocarcinoma cancer for Docetaxel 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/m² in combination with cisplatin and 5-fluorouracil

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

Tabulated list of adverse reactions in head and neck cancer for Docetaxel 75 mg/m² in combination with cisplatin and 5-fluorouracil

- Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA system organ classes	Very common adverse reactions	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 pruritus; Dry skin; Skin exfoliative (G3/4:0.6%)	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.6%)	
General disorders and administration site conditions	Lethargy (G3/4: 3.4%); Pyrexia (G3/4: 0.6%); Fluid retention; Oedema		
Investigations		Weight increased	

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA system	Very common adverse	Common adverse	Uncommon adverse

organ classes	reactions	reactions	reactions
Infections and infestation	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: 12.0%); Constipation (G3/4: 0.4%)	Dyspepsia (G3/4: 0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%); Rash pruritic	Dry skin; Desquamation	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.4%)	
General disorders and administration site conditions	Lethargy (G3/4: 4.0%); Pyrexia (G3/4: 3.6%); Fluid retention (G3/4: 1.2%); Oedema (G3/4:1.2%)		
Investigations	Weight decreased		Weight increased

Post-marketing experience

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 lachrymal duct obstruction resulting in excessive tearing have been rarely reported. Cases of cystoid macular oedema (CMO) have been reported in patients treated with docetaxel.

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

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/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure sometimes fatal have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD 02

Mechanism of action

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

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

Pharmacodynamic effects

Docetaxel was found to be cytotoxic *in vitro* against various murine and human 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

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%).

Non-small cell lung cancer

Patients previously treated with chemotherapy with or without radiotherapy

In a phase III study, in previously treated patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 75 mg/m² compared to Best Supportive Care. The 1-year survival rate was also significantly longer in docetaxel (40%) versus BSC (16%). There was less use of morphinic analgesic (p<0.01), non-morphinic analgesics (p<0.01), other disease related medications (p=0.06) and radiotherapy (p<0.01) in patients treated with docetaxel at 75 mg/m² compared to those with BSC.
The overall response rate was 6.8% in the evaluable patients, and the median duration of response was 26.1 weeks.

Docetaxel in combination with platinum agents in chemotherapy-naïve patients

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

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

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

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

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

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

Prostate cancer

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

- Docetaxel 75 mg/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.

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 α, β and γ phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

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 populations

Age and gender
A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from Phase I studies. The pharmacokinetics of docetaxel 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 ≥1.5 times the ULN associated with alkaline phosphatase ≥2.5 times the ULN), total clearance was lowered by 27% on average (see section 4.2).

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 coadministration.

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

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

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

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

Prednisone
No effect of prednisone on the pharmacokinetics of docetaxel was observed.

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate
Polysorbate 80
Ethanol, anhydrous

Solvent
Water for injections.

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

- 18 months.
- Premix solution: Chemical and physical in-use stability has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at room temperature (below 25°C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage and other handling

Do not store above 25°C .
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton contains:
- One vial of concentrate and,
- One vial of solvent

- Docetaxel Teva Pharma 80 mg vial
  15 ml clear glass Type I vial with a bromobutyl rubber stopper and a flip-off cap.

  This vial contains 2.88 ml of a 27.73 mg/ml solution of docetaxel in polysorbate 80 (fill volume: 94.4 mg/3.40 ml). This fill volume has been established during the development of docetaxel to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for docetaxel vial, there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labelled amount of 80 mg per vial.

  Solvent for Docetaxel Teva Pharma 80 mg vial
  15 ml clear glass Type I vial with a bromobutyl rubber stopper and a flip-off cap.

  Solvent vial contains 5.12 ml of water for injections (fill volume: 6.29 ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel Teva Pharma 80 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml docetaxel.

6.6 Special precautions for disposal and other handling

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

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

Preparation for the intravenous administration

a) *Preparation of the Docetaxel Teva Pharma premix solution (10 mg docetaxel/ml)*

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

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel Teva Pharma vial by partially inverting the vial.

Inject the entire contents of the syringe into the corresponding Docetaxel Teva Pharma vial.

Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.

Allow the premix vial to stand for 5 minutes at room temperature (below 25°C) and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).

The premix solution contains 10 mg/ml docetaxel and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C).

b) *Preparation of the infusion solution*

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

Inject the required premix volume into a non-PVC 250 ml infusion bag containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion.

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

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

The Docetaxel Teva Pharma infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature (below 25°C) and normal lighting conditions.

As with all parenteral products, Docetaxel Teva Pharma premix solution and 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

Teva Pharma B.V.
Computerweg 10

3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/10/662/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21st January 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Pharmachemie BV.
Swensweg 5
Postbus 552
2003 RN Haarlem
The Netherlands

TEVA Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
2100 Gödöllő
Hungary

Teva Operations Poland Sp. z.o.o.
Sienkiewicza 25
99-300 Kutno
Poland

Teva Czech Industries s.r.o
Ostravská 29
Č.p. 305
747 70 Opava-Komárov
Czech Republic

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided fro under Article 107c(7) of Directive 2001/83/EC and published on the European Medicines web-portal.

D. CONITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

- **Obligation to conduct post-authorisation measures**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 20 mg

1. NAME OF THE MEDICINAL PRODUCT

Docetaxel Teva Pharma 20 mg concentrate and solvent for solution for infusion
docetaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single-dose vial of Docetaxel Teva Pharma concentrate contains 20 mg docetaxel (anhydrous).
Each ml of concentrate contains 27.73 mg docetaxel.

3. LIST OF EXCIPIENTS

Docetaxel concentrate vial:
polysorbate 80, anhydrous ethanol.

Solvent vial:
water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate and solvent for solution for infusion.
Each carton contains:

- one vial of 0.72 ml concentrate (20 mg of docetaxel),
- one vial of 1.28 ml solvent (water for injections).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
CAUTION: Dilution of concentrate required using the entire contents of the solvent vial.
Reconstituted solution must be further diluted in the infusion diluent before administration.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC. To be administered under the supervision of a physician experienced in the use of cytotoxic agents

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Single-use vials.
Discard unused contents appropriately

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/662/001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – CONCENTRATE 20 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Docetaxel Teva Pharma 20 mg concentrate for solution for infusion
docetaxel

2. METHOD OF ADMINISTRATION

Intravenous use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.72 ml (Fill: 0.88 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – SOLVENT FOR 20 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Docetaxel Teva Pharma 20 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

water for injections
1.28 ml (Fill: 1.71 ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 80 mg

1. NAME OF THE MEDICINAL PRODUCT

Docetaxel Teva Pharma 80 mg concentrate and solvent for solution for infusion
docetaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single dose vial of Docetaxel Teva Pharma concentrate contains 80 mg docetaxel (anhydrous).
Each ml of concentrate contains 27.73 mg docetaxel.

3. LIST OF EXCIPIENTS

Docetaxel concentrate vial:
polysorbate 80, anhydrous ethanol.

Solvent vial:
water for injections.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate and solvent for solution for infusion.
Each carton contains:

- one vial (2.88 ml) of concentrate (80 mg of docetaxel),
- one vial (5.12 ml) of solvent (water for injections).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
CAUTION: Dilution of concentrate required using the entire contents of the solvent vial.
Reconstituted solution must be further diluted in the infusion diluent before administration.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

CYTOTOXIC. To be administered under the supervision of a physician experienced in the use of cytotoxic agents

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Do not freeze

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Single-use vials.
Discard unused contents appropriately

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/662/002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – CONCENTRATE 80 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Docetaxel Teva Pharma 80 mg concentrate for solution for infusion
docetaxel

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.88 ml (Fill: 3.40 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – SOLVENT FOR 80 mg

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Docetaxel Teva Pharma 80 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

water for injections
5.12 ml (Fill: 6.29 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Docetaxel Teva Pharma 20 mg concentrate and solvent for solution for infusion
docetaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, hospital pharmacist or nurse.
- If you get any side effects talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Docetaxel Teva Pharma is and what it is used for

The name of this medicine is Docetaxel Teva Pharma. Docetaxel is a substance derived from the needles of yew trees.
Docetaxel belongs to the group of anti-cancer medicines called taxoids.

Docetaxel Teva Pharma has been prescribed by your doctor for the treatment of advanced breast cancer, special forms of lung cancer (non-small cell lung cancer) and prostate cancer:
- For the treatment of advanced breast cancer, Docetaxel Teva Pharma could be administered alone.
- For the treatment of lung cancer, Docetaxel Teva Pharma could be administered either alone or in combination with cisplatin.
- For the treatment of prostate cancer, Docetaxel Teva Pharma is administered in combination with prednisone or prednisolone.

2. What you need to know before you use Docetaxel Teva Pharma

You must NOT be given Docetaxel Teva Pharma if
- you are allergic (hypersensitive) to docetaxel or any of the other ingredients of Docetaxel Teva Pharma
- the number of white blood cells is too low
- you have a severe liver disease.

Warnings and precautions

Before each treatment with Docetaxel Teva Pharma, you will have blood tests to check that you have enough blood cells and sufficient liver function to receive Docetaxel Teva Pharma. In case of white blood cells disturbances, you may experience associated fever or infections.

Tell your doctor, hospital pharmacist or nurse if you have vision problems. In case of vision problems, in particular blurred vision, you should immediately have your eyes and vision examined.

If you develop acute or worsening problems with your lungs (fever, shortness of breath or cough), please tell your doctor, hospital pharmacist or nurse immediately. Your doctor may stop your treatment immediately.

You will be asked to take premedication consisting of an oral corticosteroid such as dexamethasone, one day prior to Docetaxel Teva Pharma administration and to continue for one or two days after it in order to minimise certain undesirable effects which may occur after the infusion of Docetaxel Teva Pharma in particular allergic reactions and fluid retention (swelling of the hands, feet, legs or weight gain).

During treatment, you may be given other medicines to maintain the number of your blood cells.

Other medicines and Docetaxel Teva Pharma

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Docetaxel Teva Pharma or the other medicine may not work as well as expected and you may be more likely to get a side effect.

Pregnancy, breast-feeding and fertility

Ask your doctor for advice before being given any medicine.

Docetaxel Teva Pharma must **NOT** be administered if you are pregnant unless clearly indicated by your doctor.

You must not become pregnant during treatment with this medicine and must use an effective method of contraception during therapy because Docetaxel Teva Pharma may be harmful for the unborn baby. If pregnancy occurs during your treatment, you must immediately inform your doctor.

You must not breast-feed while you are treated with Docetaxel Teva Pharma.

If you are a man being treated with Docetaxel Teva Pharma you 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 because docetaxel may alter male fertility.

Driving and using machines

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

3. How to use Docetaxel Teva Pharma

Docetaxel Teva Pharma will be administered to you by a healthcare professional.

Usual dose

The dose will depend on your weight and your general condition. Your doctor will calculate your body surface area in square meters (m^2) and will determine the dose you should receive.

Method and route of administration

Docetaxel Teva Pharma will be given by infusion into one of your veins (intravenous use). The infusion will last approximately one hour during which you will be in the hospital.

Frequency of administration

You should usually receive your infusion once every 3 weeks.

Your doctor may change the dose and frequency of dosing depending on your blood tests, your general condition and your response to Docetaxel Teva Pharma. In particular, please inform your doctor in case of diarrhoea, sores in the mouth, feeling of numbness or pins and needles, fever and give her/him results of your blood tests. Such information will allow her/him to decide whether a dose reduction is needed. If you have any further questions on the use of this medicine, ask your doctor or hospital pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

The most commonly reported adverse reactions of Docetaxel Teva Pharma alone are: decrease in the number of red blood cells or white blood cells, alopecia, nausea, vomiting, sores in the mouth, diarrhoea and tiredness.

The severity of adverse events of Docetaxel Teva Pharma may be increased when Docetaxel Teva Pharma is given in combination with other chemotherapeutic agents.

During the infusion at the hospital the following allergic reactions **(may affect more than 1 in 10 people)**:
- flushing, skin reactions, itching
- chest tightness; difficulty in breathing
- fever or chills
- back pain
- low blood pressure.

More severe reactions may occur.

The hospital staff will monitor your condition closely during treatment. Tell them immediately if you notice any of these effects.

Between infusions of Docetaxel Teva Pharma the following may occur, and the frequency may vary with the combinations of medicines that are received:

Very common (may affect more than 1 in 10 people):
- infections, decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection) and platelets
- fever: if this happens you must tell your doctor immediately
- allergic reactions as described above
- loss of appetite (anorexia)
- insomnia
- feeling of numbness or pins and needles or pain in the joints or muscles
- headache
- alteration in sense of taste
- inflammation of the eye or increased tearing of the eyes
- swelling caused by faulty lymphatic drainage
- shortness of breath
- nasal drainage; inflammation of the throat and nose; cough
- bleeding from the nose
- sores in the mouth
- stomach upsets including nausea, vomiting and diarrhoea, constipation

- abdominal pain
- indigestion
- hair loss (in most cases normal hair growth should return)
- redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel (this may also occur on the arms, face, or body)
- change in the colour of your nails, which may detach
- muscle aches and pains; back pain or bone pain
- change or absence of menstrual period
- swelling of the hands, feet, legs
- tiredness; or flu-like symptoms
- weight gain or loss.

Common (may affect up to 1 in 10 people):
- oral candidiasis
- dehydration
- dizziness
- hearing impaired
- decrease in blood pressure; irregular or rapid heart beat
- heart failure
- oesophagatis
- dry mouth
- difficulty or painful swallowing
- haemorrhage
- raised liver enzymes (hence the need for regular blood tests).

Uncommon (may affect up to 1 in 100 people):
- fainting
- at the injection site, skin reactions, phlebitis (inflammation of the vein) or swelling
- inflammation of the colon, small intestine; intestinal perforation
- blood clots.

Frequency unknown:
- interstitial lung disease (inflammation of the lungs causing coughing and difficulty breathing. Inflammation of the lungs can also develop when docetaxel therapy is used with radiotherapy)
- pneumonia (infection of the lungs)
- pulmonary fibrosis (scarring and thickening in the lungs with shortness of breath)
- blurred vision due to swelling of the retina within the eye (cystoid macular oedema)
- decrease of the sodium in your blood.

Reporting of side effects
If you get any side effects talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Docetaxel Teva Pharma

Keep this medicine out of the sight and reach of children.

This medicine should not be used after the expiry date which is stated on the carton and vials.

Do not store above 25°C.
Do not freeze.

Store in the original package in order to protect from light.

The premix solution should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C).

The infusion solution should be used within 4 hours at room temperature (below 25°C).

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines no longer used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Docetaxel Teva Pharma concentrate vial contains:
- The active substance is docetaxel. Each vial of concentrate contains 20 mg of docetaxel. Each ml of concentrate contains 27.73 mg docetaxel.

- The other ingredients are polysorbate 80 and 25.1% (w/w) anhydrous ethanol.

What the solvent vial contains:
Water for injections.

What Docetaxel Teva Pharma looks like and contents of the pack:
Docetaxel Teva Pharma concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution.

Each carton contains:
- one 6 ml clear glass vial with a flip-off cap containing 0.72 ml concentrate and,
- one 6 ml clear glass vial with a flip-off cap containing 1.28 ml of solvent.

Marketing Authorisation Holder
Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

Manufacturer:
Pharmachemie B.V.
Swensweg 5
PO Box 552
2003 RN Haarlem
The Netherlands

TEVA Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
H-2100 Gödöllő
Hungary

Teva Operations Poland Sp. z.o.o.
Sienkiewicza 25
99-300 Kutno
Poland

Teva Czech Industries s.r.o
Ostravská 29

Č.p. 305
747 70 Opava-Komárov
Czech Republic

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland
Teva GmbH
Tel: +49 731 402 08

Eesti
Teva Eesti esindus UAB Sicor Biotech
Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς Α.Ε.
Τηλ: +30 210 72 79 099

España
Teva Pharma, S.L.U.
Tél: +34 91 387 32 80

France
Teva Santé
Tél: +33 1 55 91 78 00

Hrvatska
Pliva Hrvatska d.o.o
Tel: + 385 1 327 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 51 321 740

Ísland
ratiopharm Oy
Sími: +358 20 180 5900

Lietuva
UAB "Sicor Biotech"
Tel: +370 5 266 02 03

Luxembourg
Teva Pharma Belgium N.V./S.A./AG
Tél: +32 3 820 73 73

Magyarország
Teva Gyógyszergyár Zrt
Tel.: +36 1 288 64 00

Malta
Drugsales Ltd
Tel: +356 21 419 070/1/2

Nederland
Teva Nederland B.V.
Tel: +31 800 0228 400

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1 97007-0

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos Lda
Tel: +351 21 476 75 50

România
Teva Pharmaceuticals S.R.L
Tel: +40 21 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +421 2 5726 7911

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

Latvija
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 323 666

Suomi/Finland
ratiopharm Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +46 42 12 11 00

United Kingdom
Teva UK Limited
Tel: +44 1977 628 500

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

PREPARATION GUIDE FOR USE WITH DOCETAXEL TEVA PHARMA 20 mg CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION

It is important that you read the entire contents of this guide prior to the preparation of either the Docetaxel Teva Pharma premix solution or the Docetaxel Teva Pharma infusion solution

1. FORMULATION

Docetaxel Teva Pharma 20 mg concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution containing 27.73 mg/ml docetaxel (anhydrous) in polysorbate 80. The solvent for Docetaxel Teva Pharma is water for injections.

2. PRESENTATION

Docetaxel Teva Pharma is supplied as single-dose vials.

Each box contains one Docetaxel Teva Pharma vial (20 mg) and one corresponding solvent for Docetaxel Teva Pharma vial in a carton.

Docetaxel Teva Pharma vials should not be stored above 25°C and should be protected from light. Docetaxel Teva Pharma should not be used after the expiry date shown on the carton and vials.

2.1 Docetaxel 20 mg vial:

- The Docetaxel 20 mg vial is a 6 ml clear glass vial with a bromobutyl rubber stopper and a flip-off cap.

- The Docetaxel 20 mg vial contains a solution of docetaxel in polysorbate 80 at a concentration of 27.73 mg/ml.

- Each vial contains 20 mg/0.72 ml of a 27.73 mg/ml solution of docetaxel in polysorbate 80 (fill volume: 24.4 mg/0.88 ml). This fill volume has been established during the development of docetaxel to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for docetaxel vial, there is a minimal extractable premix volume of 2 ml containing 10 mg/ml docetaxel which corresponds to the labelled amount of 20 mg per vial.

2.2 Solvent for Docetaxel 20 mg vial:

- The solvent for Docetaxel 20 mg vial is a 6 ml clear glass vial with a bromobutyl rubber stopper and a flip-off cap.

- The solvent for Docetaxel composition is water for injections.

- Each solvent vial contains 1.28 ml of water for injections (fill volume: 1.71 ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel Teva Pharma 20mg vial ensures a premix concentration of 10 mg/ml docetaxel.

3. RECOMMENDATIONS FOR THE SAFE HANDLING

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

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

4. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

4.1 Preparation of the Docetaxel Teva Pharma premix solution (10 mg docetaxel/ml)

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

4.1.2 Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel Teva Pharma vial by partially inverting the vial.

4.1.3 Inject the entire contents of the syringe into the corresponding Docetaxel Teva Pharma vial.

4.1.4 Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.

4.1.5 Allow the premix vial to stand for 5 minutes at room temperature (below 25°C) and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).

The premix solution contains 10 mg/ml docetaxel and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between +2°C and +8°C or at room temperature (below 25°C).

4.2 Preparation of the infusion solution

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

4.2.2 Inject the required premix volume into a 250 ml non-PVC infusion bag containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

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

4.2.4 The Docetaxel Teva Pharma infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature (below 25°C) and normal lighting conditions.

4.2.5 As with all parenteral products, Docetaxel Teva Pharma premix solution and infusion solution

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

5. DISPOSAL

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures. Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Package leaflet: Information for the patient

Docetaxel Teva Pharma 80 mg concentrate and solvent for solution for infusion
docetaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, hospital pharmacist or nurse.
- If you get any side effects talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Docetaxel Teva Pharma is and what it is used for

The name of this medicine is Docetaxel Teva Pharma. Docetaxel is a substance derived from the needles of yew trees.
Docetaxel belongs to the group of anti-cancer medicines called taxoids.

Docetaxel Teva Pharma has been prescribed by your doctor for the treatment of advanced breast cancer, special forms of lung cancer (non-small cell lung cancer) and prostate cancer:
- For the treatment of advanced breast cancer, Docetaxel Teva Pharma could be administered alone.
- For the treatment of lung cancer, Docetaxel Teva Pharma could be administered either alone or in combination with cisplatin.
- For the treatment of prostate cancer, Docetaxel Teva Pharma is administered in combination with prednisone or prednisolone.

2. What you need to know before you use Docetaxel Teva Pharma

You must NOT be given Docetaxel Teva Pharma if
- you are allergic (hypersensitive) to docetaxel or any of the other ingredients of Docetaxel Teva Pharma
- the number of white blood cells is too low
- you have a severe liver disease.

Warnings and precautions

Before each treatment with Docetaxel Teva Pharma, you will have blood tests to check that you have enough blood cells and sufficient liver function to receive Docetaxel Teva Pharma. In case of white blood cells disturbances, you may experience associated fever or infections.

Tell your doctor, hospital pharmacist or nurse if you have vision problems. In case of vision problems, in particular blurred vision, you should immediately have your eyes and vision examined.

If you develop acute or worsening problems with your lungs (fever, shortness of breath or cough), please tell your doctor, hospital pharmacist or nurse immediately. Your doctor may stop your treatment immediately.

You will be asked to take premedication consisting of an oral corticosteroid such as dexamethasone, one day prior to Docetaxel Teva Pharma administration and to continue for one or two days after it in order to minimise certain undesirable effects which may occur after the infusion of Docetaxel Teva Pharma in particular allergic reactions and fluid retention (swelling of the hands, feet, legs or weight gain).

During treatment, you may be given other medicines to maintain the number of your blood cells.

Other medicines and Docetaxel Teva Pharma

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because Docetaxel Teva Pharma or other medicine may not work as well as expected and you may be more likely to get a side effect.

Pregnancy, breast-feeding and fertility

Ask your doctor for advice before being given any medicine.

Docetaxel Teva Pharma must **NOT** be administered if you are pregnant unless clearly indicated by your doctor.

You must not become pregnant during treatment with this medicine and you must use an effective method of contraception during therapy because Docetaxel Teva Pharma may be harmful for the unborn baby. If pregnancy occurs during your treatment, you must immediately inform your doctor.

You must not breast-feed while you are treated with Docetaxel Teva Pharma.

If you are a man being treated with Docetaxel Teva Pharma you 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 because docetaxel may alter male fertility.

Driving and using machines

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

3. How to use Docetaxel Teva Pharma

Docetaxel Teva Pharma will be administered to you by a healthcare professional.

Usual dose

The dose will depend on your weight and your general condition. Your doctor will calculate your body surface area in square meters (m^2) and will determine the dose you should receive.

Method and route of administration

Docetaxel Teva Pharma will be given by infusion into one of your veins (intravenous use). The infusion will last approximately one hour during which you will be in the hospital.

Frequency of administration

You should usually receive your infusion once every 3 weeks.

Your doctor may change the dose and frequency of dosing depending on your blood tests, your general condition and your response to Docetaxel Teva Pharma. In particular, please inform your doctor in case of diarrhoea, sores in the mouth, feeling of numbness or pins and needles, fever and give her/him results of your blood tests. Such information will allow her/him to decide whether a dose reduction is needed. If you have any further questions on the use of this medicine, ask your doctor or hospital pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss these with you and will explain the potential risks and benefits of your treatment.

The most commonly reported adverse reactions of Docetaxel Teva Pharma alone are: decrease in the number of red blood cells or white blood cells, alopecia, nausea, vomiting, sores in the mouth, diarrhoea and tiredness.

The severity of adverse events of Docetaxel Teva Pharma may be increased when Docetaxel Teva Pharma is given in combination with other chemotherapeutic agents.

During the infusion at the hospital the following allergic reactions **(may affect more than 1 in 10 people)**:
- flushing, skin reactions, itching
- chest tightness; difficulty in breathing
- fever or chills
- back pain
- low blood pressure.

More severe reactions may occur.

The hospital staff will monitor your condition closely during treatment. Tell them immediately if you notice any of these effects.

Between infusions of Docetaxel Teva Pharma the following may occur, and the frequency may vary with the combinations of medicines that are received:

Very common (may affect more than 1 in 10 people):
- infections, decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection) and platelets
- fever: if this happens you must tell your doctor immediately
- allergic reactions as described above
- loss of appetite (anorexia)
- insomnia
- feeling of numbness or pins and needles or pain in the joints or muscles
- headache
- alteration in sense of taste
- inflammation of the eye or increased tearing of the eyes
- swelling caused by faulty lymphatic drainage
- shortness of breath
- nasal drainage; inflammation of the throat and nose; cough
- bleeding from the nose
- sores in the mouth
- stomach upsets including nausea, vomiting and diarrhoea, constipation

- abdominal pain
- indigestion
- hair loss (in most cases normal hair growth should return)
- redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel (this may also occur on the arms, face, or body)
- change in the colour of your nails, which may detach
- muscle aches and pains; back pain or bone pain
- change or absence of menstrual period
- swelling of the hands, feet, legs
- tiredness; or flu-like symptoms
- weight gain or loss.

Common (may affect up to 1 in 10 people):
- oral candidiasis
- dehydration
- dizziness
- hearing impaired
- decrease in blood pressure; irregular or rapid heart beat
- heart failure
- oesophagatis
- dry mouth
- difficulty or painful swallowing
- haemorrhage
- raised liver enzymes (hence the need for regular blood tests).

Uncommon (may affect up to 1 in 100 people):
- fainting
- at the injection site, skin reactions, phlebitis (inflammation of the vein) or swelling
- inflammation of the colon, small intestine; intestinal perforation
- blood clots.

Frequency unknown:
- interstitial lung disease (inflammation of the lungs causing coughing and difficulty breathing. Inflammation of the lungs can also develop when docetaxel therapy is used with radiotherapy)
- pneumonia (infection of the lungs)
- pulmonary fibrosis (scarring and thickening in the lungs with shortness of breath)
- blurred vision due to swelling of the retina within the eye (cystoid macular odema)
- decrease of the sodium in your blood.

Reporting of side effects
If you get any side effects talk to your doctor, hospital pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Docetaxel Teva Pharma

Keep this medicine out of the sight and reach of children.

This medicine should not be used after the expiry date which is stated on the carton and vials.

Do not store above 25°C.
Do not freeze.

Store in the original package in order to protect from light.

The premix solution should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C).

The infusion solution should be used within 4 hours at room temperature (below 25°C).

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines no longer used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Docetaxel Teva Pharma concentrate vial contains:
- The active substance is docetaxel. Each vial of concentrate contains 80 mg of docetaxel. Each ml of concentrate contains 27.73 mg docetaxel.

- The other ingredients are polysorbate 80 and 25.1% (w/w) anhydrous ethanol.

What the solvent vial contains:
Water for injections.

What Docetaxel Teva Pharma looks like and contents of the pack:
Docetaxel Teva Pharma concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution.

Each carton contains:
- one 15 ml clear glass vial with a flip-off cap containing 2.88 ml concentrate and,
- one 15 ml clear glass vial with a flip-off cap containing 5.12 ml of solvent.

Marketing Authorisation Holder
Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

Manufacturer:
Pharmachemie B.V.
Swensweg 5
PO Box 552
2003 RN Haarlem
The Netherlands

TEVA Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
2100 Gödöllő
Hungary

Teva Operations Poland Sp. z.o.o.
Sienkiewicza 25
99-300 Kutno
Poland

Teva Czech Industries s.r.o
Ostravská 29

Č.p. 305
747 70 Opava-Komárov
Czech Republic

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

България
Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika
Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark
Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland
Teva GmbH
Tel: +49 731 402 08

Eesti
Teva Eesti esindus UAB Sicor Biotech
Eesti filiaal
Tel: +372 661 0801

Ελλάδα
Teva Ελλάς Α.Ε.
Τηλ: +30 210 72 79 099

España
Teva Pharma, S.L.U.
Tél: +34 91 387 32 80

France
Teva Santé
Tél: +33 1 55 91 78 00

Hrvatska
Pliva Hrvatska d.o.o
Tel: + 385 1 37 20 000

Ireland
Teva Pharmaceuticals Ireland
Tel: +353 51 321 740

Ísland
ratiopharm Oy
Sími: +358 20 180 5900

Lietuva
UAB "Sicor Biotech"
Tel: +370 5 266 02 03

Luxembourg
Teva Pharma Belgium N.V./S.A./AG
Tél: +32 3 820 73 73

Magyarország
Teva Gyógyszergyár Zrt.
Tel.: +36 1 288 64 00

Malta
Drugsales Ltd
Tel: +356 21 419 070/1/2

Nederland
Teva Nederland B.V.
Tel: +31 800 0228 400

Norge
Teva Norway AS
Tlf: +47 66 77 55 90

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
Tel: +43 1 97007 0

Polska
Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

Portugal
Teva Pharma - Produtos Farmacêuticos Lda
Tel: +351 21 476 75 50

România
Teva Pharmaceuticals S.R.L
Tel: +40 21 230 65 24

Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika
Teva Pharmaceuticals Slovakia s.r.o.
Tel: +421 2 5726 7911

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

Latvija
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 323 666

Suomi/Finland
ratiopharm Oy
Puh/Tel: +358 20 180 5900

Sverige
Teva Sweden AB
Tel: +46 42 12 11 00

United Kingdom
Teva UK Limited
Tel: +44 1977 628 500

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

PREPARATION GUIDE FOR USE WITH DOCETAXEL TEVA PHARMA 80 mg CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION

It is important that you read the entire contents of this guide prior to the preparation of either the Docetaxel Teva Pharma premix solution or the Docetaxel Teva Pharma infusion solution

1. FORMULATION

Docetaxel Teva Pharma 80 mg concentrate for solution for infusion is a clear viscous, yellow to brown-yellow solution containing 27.73 mg/ml docetaxel (anhydrous) in polysorbate 80. The solvent for Docetaxel Teva Pharma is water for injections.

2. PRESENTATION

Docetaxel Teva Pharma is supplied as single-dose vials.

Each box contains one Docetaxel Teva Pharma vial (80 mg) and one corresponding solvent for Docetaxel Teva Pharma vial in a carton.

Docetaxel Teva Pharma vials should not be stored above 25°C and should be protected from light. Docetaxel Teva Pharma should not be used after the expiry date shown on the carton and vials.

2.1 Docetaxel 80 mg vial:

- The Docetaxel 80 mg vial is a 15 ml clear glass vial with a bromobutyl rubber stopper and a flip-off cap.

- The Docetaxel 80 mg vial contains a solution of docetaxel in polysorbate 80 at a concentration of 27.73 mg/ml.

  Each vial contains 80 mg/2.88 ml of a 27.73 mg/ml solution of docetaxel in polysorbate 80 (fill volume: 94.4 mg/3.40 ml). This fill volume has been established during the development of

docetaxel to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for docetaxel vial, there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labelled amount of 80 mg per vial.

2.2 Solvent for Docetaxel 80 mg vial:

- The solvent for Docetaxel 80 mg vial is a 15 ml clear glass vial with a bromobutyl rubber stopper and a flip-off cap.

- The solvent for Docetaxel composition is water for injections.

  Each solvent vial contains 5.12 ml of water for injections (fill volume: 6.29 ml). The addition of the entire contents of the solvent vial to the contents of the docetaxel 80 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml docetaxel.

3. RECOMMENDATIONS FOR THE SAFE HANDLING

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

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

4. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

4.1 Preparation of the Docetaxel Teva Pharma premix solution (10 mg docetaxel/ml)

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

4.1.2 Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel Teva Pharma vial by partially inverting the vial.

4.1.3 Inject the entire contents of the syringe into the corresponding Docetaxel Teva Pharma vial.

4.1.4 Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.

4.1.5 Allow the premix vial to stand for 5 minutes at room temperature (below 25°C) and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).

The premix solution contains 10 mg/ml docetaxel and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between +2°C and +8°C or at room temperature (below 25°C).

4.2 Preparation of the infusion solution

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

4.2.2 Inject the required premix volume into a 250 ml non-PVC infusion bag containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

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

4.2.4 The Docetaxel Teva Pharma infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature (below 25°C) and normal lighting conditions.

4.2.5 As with all parenteral products, Docetaxel Teva Pharma premix solution and infusion solution

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

5. DISPOSAL

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures. Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.