1 NAME OF THE MEDICINAL PRODUCT

Hospira Docetaxel Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL contains 10 mg docetaxel.

One vial of 2 mL contains 20 mg docetaxel (for single-dose application).

One vial of 8 mL contains 80 mg docetaxel (for single-dose application).

Excipient with known effect

Each vial contains ethanol anhydrous 182 mg/mL (23% v/v). See Section 4.4 Special warnings and precautions for use - Alcohol content.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion

A clear colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

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

- Hospira Docetaxel Concentrate for Solution for Infusion 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.

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

Non-small cell lung cancer

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

- Hospira Docetaxel Concentrate for Solution for Infusion 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

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

Gastric adenocarcinoma

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

Head and neck cancer

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

Ovarian cancer

Hospira Docetaxel Concentrate for Solution for Infusion is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.

4.2 Posology and method of administration

Hospira Docetaxel Concentrate for Solution for Infusion is for intravenous use only.

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

Recommended dosage

For breast, non-small cell lung, ovarian, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used (see Section 4.4). Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

For prostate cancer, given the concurrent use of prednisone or prednisolone the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see Section 4.4).

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

Breast cancer

For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dosage of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).

In combination with capecitabine, the recommended dose of docetaxel is 75 mg/m^2 every three weeks, combined with capecitabine at 1,250 mg/m^2 twice daily (within 30 minutes after a meal) for 2 weeks

followed by 1-week rest period. For capecitabine dose calculation according to body surface area, see capecitabine summary of product characteristics.

Non-small cell lung cancer

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

Prostate cancer

Hormone refractory metastatic prostate cancer

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

Gastric adenocarcinoma

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

Head and neck cancer

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

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

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

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

Ovarian cancer

The recommended dosage of docetaxel is 100 mg/m^2 administered as a one-hour infusion every three weeks.

Dosage 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 <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 75 mg/m^2 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, 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 dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see manufacturer's summary of product characteristics.

In combination with capecitabine

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

In combination with cisplatin and 5-fluorouracil

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

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

Toxicity	**Dosage adjustment**
Diarrhoea Grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.
Diarrhoea Grade 4	First episode: reduce docetaxel and 5-FU doses by 20%. Second episode: discontinue treatment.

Toxicity	Dosage adjustment
Stomatitis/mucositis Grade 3	First episode: reduce 5-FU dose by 20%. Second episode: stop 5-FU only, at all subsequent cycles. Third episode: reduce docetaxel dose by 20%.
Stomatitis/mucositis Grade 4	First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%.

For cisplatin and 5-fluorouracil dosage adjustments, see manufacturers' summary of product characteristics.

In the pivotal trial in patients who received an induction treatment with docetaxel for inoperable locally advanced squamous SCCHN and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g., day 6-15) in all subsequent cycles.

Special populations

Patients with hepatic impairment

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

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

Children and adolescents

The experience in children and adolescents is limited.

Elderly

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

In combination with capecitabine, for patients 60 years of age or more, a starting dose reduction of capecitabine to 75% is recommended (see capecitabine summary of product characteristics).

4.3 Contraindications

Docetaxel is contraindicated in patients who:

- Have a history of known hypersensitivity to docetaxel or any of the excipients.
- Have a baseline neutrophil count of <1,500 cells/mm^3.
- Are pregnant (see Section 4.6).
- Are breast-feeding (see Section 4.6).
- Have 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

Premedication

Patients should be pre-treated prior to docetaxel administration. 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

Bone marrow suppression and other haematological effects of docetaxel include neutropenia, 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 in all patients receiving docetaxel. Patients should be retreated with docetaxel when neutrophils recover to a level of ≥1,500 cells/mm^3 (see Section 4.2).

Hospira Docetaxel Concentrate for Solution for Infusion should not be administered to patients with baseline neutrophil counts of <1,500 cells/mm^3. Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel. Patients should not be retreated with Hospira Docetaxel Concentrate for Solution for Infusion until neutrophils recover to a level greater than or equal to 1,500 cells/mm^3.

In the case of severe neutropenia (<500 cells/mm^3 for 7 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 (TPF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G-CSF. Patients treated with TPF should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TPF should be closely monitored (see Sections 4.2 and 4.8).

Gastrointestinal reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications (see Sections 4.2, 4.4 and 4.8). Although majority of cases occurred during the first or second cycle of docetaxel-containing regimen, enterocolitis could develop at any time, and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity.

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 of, during or immediately following the cessation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. Frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised

rash/erythema require immediate discontinuation of docetaxel and aggressive therapy. Severe symptoms are usually resolved after discontinuing the infusion and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with docetaxel. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of docetaxel therapy.

Cutaneous reactions

Reversible cutaneous reactions were generally mild to moderate. Reactions were characterised by a rash including localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation but also arms, face or thorax, and frequently associated with pruritus has been observed. 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 have been reported (see Section 4.2). Nail disorders were characterised by hypopigmentation or hyperpigmentation, pain and onycholysis.

Very rare cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, scleroderma-like changes and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) have been reported with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear, discontinuation of docetaxel should be considered. In some cases, multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects.

Ear and labyrinth disorders

Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Fluid retention

A premedication consisting of an oral corticosteroid, e.g., dexamethasone 16 mg per day (e.g., 8 mg twice daily) for three days starting one day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

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; however, it has been reported in some patients during early courses of therapy. The median cumulative dose to onset for treatment with 75 mg/m^2 is 524 mg/m^2 and treatment at 100 mg/m^2 is 509 mg/m^2 (without premedication) and 797 mg/m^2 (with premedication). Fluid retention is slowly reversible after docetaxel treatment is stopped. In patients treated by docetaxel as single agent at 100 mg/m^2, 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).

Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

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

Patients developing peripheral oedema may be treated with standard measures.

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.

Eye disorders

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

Tumour lysis syndrome

Tumour lysis syndrome has been reported with docetaxel after the first or the second cycle (see Section 4.8). Patients at risk of tumour lysis syndrome (e.g., with renal impairment, hyperuricemia, bulky tumour, rapid progression) should be closely monitored. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

CYP3A4 inhibitors

The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see Section 4.5).

Alcohol content

Hospira Docetaxel Concentrate for Solution for Infusion contains ethanol.

The alcohol content is harmful for those suffering from alcoholism.

The alcohol content is to be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

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

Co-administration with medicines containing e.g., propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity.

Patients with hepatic 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 death 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, a pivotal clinical trial excluded patients with ALT and/or AST >1.5 times ULN associated with alkaline phosphatase >2.5 times ULN and bilirubin >1 times ULN; for these patients, no dose reductions can be recommended and docetaxel should not be used unless strictly indicated.

No data are available in patients with hepatic impairment treated by docetaxel in combination in the other indications.

Patients with renal impairment

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

Hospira Docetaxel Concentrate for Solution for Infusion contains PEG300 which may increase the risk of nephrotoxicity in patients with renal impairment.

Nervous system

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

Since docetaxel contains ethanol (182 mg/mL), consideration should be given to possible central nervous system and other effects. The amount of alcohol in this medicinal product may alter the effects of other medicines.

Others

Contraceptive measures must be taken by both men and women (see Section 4.6).

Paediatric use

The safety and effectiveness of docetaxel in children have not been established.

Use in elderly

An analysis of safety data in patients equal to or greater than 60 years of age treated with docetaxel in combination with capecitabine showed an increase in the incidence of treatment-related Grade 3 or 4 adverse effects, treatment-related serious adverse effects and early withdrawals from treatment due to adverse effects compared to patients less than 60 years of age.

Use in hormone refractory metastatic prostate cancer

Of the 333 patients treated with docetaxel every three weeks for hormone refractory metastatic prostate cancer in the prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. Differences in efficacy were not identified between elderly patients and younger patients. In patients treated with docetaxel every three weeks, the incidence of anaemia, infection, nail changes, anorexia, weight loss occurred at rates greater than or equal to 10% higher in patients who were 65 years of age or greater compared to younger patients.

Use in combination with cisplatin and 5-fluorouracil (TPF) for SCCHN

Of the 174 and 251 patients who received the induction treatment with docetaxel in combination with cisplatin and 5-fluorouracil (TPF) for SCCHN in the TAX 323 and TAX 324 studies, only 18 (10%)

and 32 (13%), respectively, of the patients were 65 years of age or older. The number of elderly patients who received this regimen was not sufficient to determine whether geriatric patients responded differently from younger patients. Elderly patients treated with TPF should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal clinical studies to evaluate the drug interactions of docetaxel.

In vitro studies suggest that isoenzymes of the cytochrome P450 3A subfamily appear to be involved in the hepatic metabolism of docetaxel in humans. *In vitro,* the 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 ciclosporin, terfenadine, ketoconazole, erythromycin and troleandomycin and to a lesser extent by doxorubicin, vinorelbine, vinblastine and nifedipine, increased by dexamethasone, phenobarbitone and clofibrate and unaffected by cimetidine, ranitidine, omeprazole, diazepam, imipramine, paracetamol, caffeine, tolbutamide and quinidine. Strong P450 3A inhibitors may affect docetaxel metabolism *in vivo*, as a result, caution should be exercised when treating patients with these drugs as concomitant therapy since there is a potential for a significant interaction.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration.

In vitro, docetaxel is highly protein bound (>95%), with the important proteins being albumin, alpha1-acid glycoprotein and lipoproteins. Although the possible *in vivo* interaction of docetaxel with concomitantly administered medication 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.

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 has been 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.

In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49%.

In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided. If the concomitant use of a strong CYP3A4 inhibitor cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during concomitant treatment with the strong CYP3A4 inhibitor.

In vivo investigations show that caution should be exercised when administering ketoconazole to patients as concomitant therapy since there is a potential for a significant interaction. Docetaxel should be administered with caution in patients concomitantly receiving protease inhibitors (e.g., ritonavir) which are inhibitors and substrates of cytochrome P450 3A.

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

4.6 Pregnancy and lactation

Pregnancy

As with other cytotoxic drugs, docetaxel may cause fetal harm when administered to pregnant women. Therefore, docetaxel should not be used during pregnancy unless the clinical condition of the woman requires treatment with docetaxel.

Fetal radioactivity has been detected following intravenous administration of radiolabelled docetaxel to pregnant rats. *In vivo* studies have shown docetaxel to be both embryotoxic and fetotoxic in rabbits and rats (see Section 5.3). At intravenous doses of 0.9 mg/m^2, docetaxel caused fewer corpora lutea, fewer implantations, increased resorptions and embryofetal deaths in rats. No evidence of teratogenic effects was found when docetaxel was administered intravenously at doses up to 1.8 mg/m^2 or 1.2 mg/m^2 in rats or rabbits, respectively, but reduced fetal weight and delayed ossification were observed.

Offspring from rats receiving docetaxel 1.5 mg/m^2/day intravenously from late gestation until weaning showed signs of delayed development. There is no information on the use of docetaxel in pregnant women.

If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard. Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Contraception in males and females

Based on reproductive toxicity and genetic toxicity findings, women of childbearing potential should be advised to use effective contraception during treatment with docetaxel and for at least 2 months after the last dose.

Based on genetic toxicity findings, male patients with female partners of childbearing potential should be advised to use effective contraception during treatment with docetaxel and for at least 4 months after the last dose.

Lactation

Radioactivity has been detected in milk following intravenous administration of radiolabelled docetaxel to lactating rats. Offspring from rats receiving docetaxel 1.5 mg/m^2/day intravenously during late gestation and lactation showed signs of delayed development. 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 and for 1 week after the last dose.

Fertility

Studies in mice have shown that intravenous doses of 144 mg/m^2 or 30 mg/m^2/day for five days are associated with testicular atrophy, mineralisation and degeneration of tubular germinal epithelium, Leydig cell hyperplasia and epididymal hypospermia and follicular atresia in the ovaries. Studies in rats have shown that intravenous doses of 120 mg/m^2 are associated with testicular atrophy, germ cell atrophy, Leydig cell hyperplasia and mineralisation. The rodent studies suggest that docetaxel may impair fertility. Studies in rats have also shown that intravenous doses of 0.9 mg/m^2/day to both sexes are associated with reduced litter averages for corpora lutea, implantations and live fetuses, and increased litter averages for early and total resorptions. Larger doses to both sexes (males 1.8 mg/m^2/day, females 1.35 mg/m^2/day) are additionally associated with increased time to mating, increased number of dams with total resorption, and reduced male fetal bodyweight.

An adverse effect on male or female fertility cannot be excluded. Therefore, men being treated with docetaxel are advised to seek advice on conservation of sperm prior to treatment, and all patients intending to have a child after treatment are advised to consider individual genetic counselling.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. Patients should refrain from driving or using machines until they know that the docetaxel does not negatively affect these abilities.

The amount of ethanol in docetaxel may impair the ability to drive or use machines. The alcohol content in a maximum recommended dose of 200 mg (based on 100 mg/m^2, body surface area 2.0 m^2) contains approximately 1.8 g of absolute ethanol.

4.8 Undesirable effects

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

- 1,312 and 121 patients who receive 100 mg/m^2 and 75 mg/m^2 of docetaxel as a single agent respectively.
- 258 patients who received docetaxel in combination with doxorubicin.
- 406 patients who received docetaxel in combination with cisplatin.
- 92 patients treated with docetaxel in combination with trastuzumab.
- 255 patients who received docetaxel in combination with capecitabine.
- 332 patients who received docetaxel in combination with prednisone or prednisolone (clinically important treatment-related adverse events are presented).
- 300 gastric adenocarcinoma patients (221 patients in Phase III part of the study and 79 patients in the Phase II part) who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment-related adverse events are presented).
- 174 and 251 head and neck cancer patients who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment-related adverse events are presented).

These reactions were described using the NCI Common Toxicity Criteria (Grade 3 = G3; Grade 3-4 = G3/4; Grade 4 = G4) and the COSTART terms. Frequencies are defined as very common (≥1/10), common (≥1/100 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 capecitabine, the most frequent treatment-related undesirable effects (≥5%) reported in a Phase III trial in breast cancer patients failing anthracycline treatment are presented (see capecitabine Summary of Product Characteristics).

The following adverse reactions are frequently observed with docetaxel:

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 paraesthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

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

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 hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Fluid retention includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity (see Section 4.4).

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 drug fever or chills. Severe reactions were characterised by hypotension and/or bronchospasm or generalised rash/erythema (see Section 4.4).

Docetaxel 100 mg/m^2 single agent

MedDRA system organ classes	**Very common adverse reactions ≥10% of patients**	**Common adverse reactions ≥1 to <10% of patients**	**Uncommon adverse reactions ≥0.1 to <1% of patients**
Investigations		G3/4 Blood bilirubin increased (<5%) G3/4 Blood alkaline phosphatase increased (<4%) G3/4 AST increased (<3%) G3/4 ALT increased (<2%)	
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure (0.5%)
Blood and the lymphatic system disorders	Neutropenia (G4: 76.4%) Anaemia (G3/4: 8.9%) Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	

Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%) Peripheral motor neuropathy (G3/4: 4%) Dysgeusia (severe 0.07%)		
Respiratory, thoracic and mediastinal disorders	Dyspnoea (severe 2.7%)		
Gastrointestinal disorders	Stomatitis (G3/4: 5.3%) Diarrhoea (G3/4: 4%) Nausea (G3/4: 4%) Vomiting (G3/4: 3%)	Constipation (severe 0.2%) Abdominal pain (severe 1%) Gastrointestinal haemorrhage (severe 0.3%)	Oesophagitis (severe 0.4%)
Skin and subcutaneous tissue disorders	Alopecia Skin reaction (G3/4: 5.9%) Nail disorders (severe 2.6%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe 1.4%)	Arthralgia	
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Vascular disorders		Hypotension Hypertension Haemorrhage	
General disorders and administration site conditions	Fluid retention (severe: 6.5%) Asthenia (severe 11.2%) Pain	Infusion site reaction Non-cardiac chest pain (severe 0.4%)	
Immune system disorders	Hypersensitivity (G3/4: 5.3%)		

Blood and lymphatic system disorders

Rare: bleeding episodes associated with Grade 3/4 thrombocytopenia.

Nervous system disorders

Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 100 mg/m^2 as single agent. The events were spontaneously reversible within 3 months.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

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

Docetaxel 75 mg/m^2 single agent

MedDRA system organ classes	Very common adverse reactions ≥10% of patients	Common adverse reactions ≥1 to <10% of patients
Investigations		G3/4 Blood bilirubin increased (<2%)
Cardiac disorders		Arrhythmia (not severe)
Blood and the lymphatic system disorders	Neutropenia (G4: 54.2%) Anaemia (G3/4: 10.8%) Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Gastrointestinal disorders	Nausea (G3/4: 3.3%) Stomatitis (G3/4: 1.7%) Vomiting (G3/4: 0.8%) Diarrhoea (G3/4: 1.7%) Mucositis	Constipation
Skin and subcutaneous tissue disorders	Alopecia Skin reaction (G3/4: 0.8%)	Nail disorders (severe 0.8%)
Musculoskeletal and connective tissue disorders		Myalgia
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infections (G3/4: 5%)	
Vascular disorders		Hypotension
General disorders and administration site conditions	Asthenia (severe 12.4%) Fluid retention (severe 0.8%) Pain	
Immune system disorders		Hypersensitivity (not severe)

Docetaxel 75 mg/m^2 in combination with doxorubicin

MedDRA system organ classes	Very common adverse reactions ≥10% of patients	Common adverse reactions ≥1 to <10% of patients	Uncommon adverse reactions ≥0.1 to <1% of patients
Investigations		G3/4 Blood bilirubin increased (<2.5%) G3/4 Blood alkaline Phosphatase increased (<2.5%)	G3/4 AST increased (<1%) G3/4 ALT increased (<1%)
Cardiac disorders		Cardiac failure Arrhythmia (not severe)	
Blood and the lymphatic system disorders	Neutropenia (G4: 91.7%) Anaemia (G3/4: 9.4%) Febrile neutropenia Thrombocytopenia (G4: 0.8%)		
Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Gastrointestinal disorders	Nausea (G3/4: 5%) Stomatitis (G3/4: 7.8%) Diarrhoea (G3/4: 6.2%) Vomiting (G3/4: 5%) Constipation		
Skin and subcutaneous tissue disorders	Alopecia Nail disorders (severe 0.4%) Skin reaction (not severe)		
Musculoskeletal and connective tissue disorders		Myalgia	
Metabolism and nutrition disorders		Anorexia	
Infections and infestations	Infection (G3/4: 7.8%)		
Vascular disorders			Hypotension

General disorders and administration site conditions	Asthenia (severe 8.1%) Fluid retention (severe 1.2%) Pain	Infusion site reaction	
Immune system disorders		Hypersensitivity (G3/4: 1.2%)	

Docetaxel 75 mg/m^2 in combination with cisplatin

MedDRA system organ classes	Very common adverse reactions ≥10% of patients	Common adverse reactions ≥1 to <10% of patients	Uncommon adverse reactions ≥0.1 to <1% of patients
Investigations		G3/4 Blood bilirubin increased (2.1%) G3/4 ALT increased (1.3%)	G3/4 AST increased (0.5%) G3/4 Blood alkaline phosphatase increased (0.3%)
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Blood and the lymphatic system disorders	Neutropenia (G4: 51.5%) Anaemia (G3/4: 6.9%) Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%) Peripheral motor neuropathy (G3/4: 2%)		
Gastrointestinal disorders	Nausea (G3/4: 9.6%) Vomiting (G3/4: 7.6%) Diarrhoea (G3/4: 6.4%) Stomatitis (G3/4: 2%)	Constipation	
Skin and subcutaneous tissue disorders	Alopecia Nail disorders (severe 0.7%) Skin reaction (G3/4: 0.2%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe 0.5%)		
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infection (G3/4: 5.7%)		
Vascular disorders		Hypotension (G3/4: 0.7%)	
General disorders and administration site conditions	Asthenia (severe 9.9%) Fluid retention (severe 0.7%) Pyrexia (G3/4: 1.2%)	Infusion site reaction pain	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		

Docetaxel 75 mg/m^2 in combination with capecitabine

MedDRA system organ classes	Very common adverse reactions ≥10% of patients	Common adverse reactions ≥1 to <10% of patients
Investigations	Increased alkaline phosphatase (G3/4: 1%) Increased AST (G3/4: 3%) Increased ALT (G3/4: 2%)	Weight decreased G3/4 Blood bilirubin increased (9%) Serum creatinine (G3/4: <1%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 63%) Anaemia (G3/4: 10%) Decreased haemoglobin (G3/4: 4%) Neutropenic fever (G3/4: 16%)	Thrombocytopenia (G3/4: 3%) Leucopenia (G3/4: 3%)
Nervous system disorders	Dysgeusia (G3/4: <1%) Paraesthesia (G3/4: <1%)	Dizziness Headache (G3/4: <1%) Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%) Sore throat	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%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%) Decreased appetite	Dehydration (G3/4: 2%)
Infections and infestations		Oral candidiasis (G3/4: <1%)
General disorders and administration site conditions	Asthenia (G3/4: 3%) Pyrexia (G3/4: 1%) Fatigue/weakness (G3/4: 5%) Oedema Peripheral (G3/4: 1%)	Lethargy Pain

Docetaxel 75 mg/m^2 in combination with prednisone or prednisolone

MedDRA system organ classes	**Very common adverse reactions ≥10% of patients**	**Common adverse reactions ≥1 to <10% of patients**
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%) Anaemia (G3/4: 4.9%)	Thrombocytopenia; (G3/4: 0.6%) Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%) Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G3/4: 0.6%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%) Dyspnoea (G3/4: 0.6%) Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%) Diarrhoea (G3/4: 1.2%) Stomatitis/Pharyngitis (G3/4: 0.9%) Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia Nail disorders (not severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue disorders		Arthralgia (G3/4: 0.3%) Myalgia (G3/4: 0.3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Infections and infestations	Infection (G3/4: 3.3%)	
General disorders and administration site conditions	Fatigue (G3/4: 3.9%) Fluid retention (severe 0.6%)	
Immune system disorders		Hypersensitivity (G3/4: 0.6%)

Docetaxel 75 mg/m^2 in combination with cisplatin and 5-fluorouracil for gastric adenocarcinoma cancer

MedDRA system organ classes	**Very common adverse reactions ≥10% of patients**	**Common adverse reactions ≥1 to <10% of patients**
Cardiac disorders		Arrhythmia (G3/4: 1.0%)
Blood and the lymphatic system disorders	Anaemia (G3/4: 20.9%) Neutropenia (G3/4: 83.2%) Thrombocytopenia (G3/4: 8.8%) Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 8 7%)	Dizziness (G3/4: 2.3%) Peripheral motor neuropathy (G3/4: 1.3%)
Eye disorders		Lacrimation increased (G3/4: 0%)

Ear and labyrinth disorders		Hearing impaired (G3/4: 0%)
Gastrointestinal disorders	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%)	Pruritic rash (G3/4: 0.7%) Nail disorders (G3/4: 0.7%) Skin exfoliation (G3/4: 0%)
Metabolism and nutrition disorders	Anorexia (G3/4: 11.7%)	
Infections and infestations	Neutropenic infection Infection (G3/4: 11.7%)	
General disorders and administration site conditions	Lethargy (G3/4: 19.0%) Pyrexia (G3/4: 2.3%) Fluid retention (severe/life-threatening: 1%)	
Immune system disorders	Hypersensitivity (G3/4: 1.7)	

Blood and the lymphatic system disorders

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

Docetaxel 75 mg/m^2 in combination with cisplatin and 5-fluorouracil for head and neck cancer

Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA system organ classes	**Very common adverse reactions ≥10% of patients**	**Common adverse reactions ≥1 to <10% of patients**	**Uncommon adverse reactions ≥0.1 to <1% of patients**
Investigations		Weight increased Weight loss	
Cardiac disorders		Myocardial ischaemia (G3/4: 1.7%)	Arrhythmia (G3/4: 0.6%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 76.3%) Anaemia (G3/4: 9.2%) Thrombocytopenia (G3/4: 5.2%)	Febrile neutropenia*	
Nervous system disorders	Dysgeusia/Parosmia Peripheral sensory neuropathy (G3/4: 0.6%)	Dizziness	
Eye disorders		Lacrimation increased Conjunctivitis	
Ear and labyrinth disorders		Hearing impaired	
Gastrointestinal disorders	Nausea (G3/4: 0.6%) Stomatitis (G3/4: 4.0%) Diarrhoea (G3/4: 2.9%) Vomiting (G3/4: 0.6%)	Constipation Oesophagitis/dysphagia /odynophagia (G3/4: 0.6%) Abdominal pain Dyspepsia Gastrointestinal haemorrhage (G3/4: 0.6%) Gastrointestinal pain/cramping	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 10.9%)	Pruritic rash Dry skin Skin exfoliative (G3/4: 0.6%)	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.6%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)		

Infections and infestations	Infection (G3/4: 6.3%) Neutropenic infection		
Neoplasms benign and malignant (including cysts and polyps)		Cancer pain (G3/4: 0.6%)	
Vascular disorders		Venous disorder (G3/4:0.6%)	
General disorders and administration site conditions	Lethargy (G3/4: 3.4%) Pyrexia (G3/4: 0.6%) Fluid retention Oedema		
Immune system disorders		Hypersensitivity (not severe)	

* Febrile neutropenia: grade ≥2 fever concomitant with Grade 4 neutropenia requiring I.V antibiotics and/or hospitalisation. Clinically important TEAEs were determined based upon frequency, severity and clinical impact of the adverse event.

Induction chemotherapy followed by radiotherapy (TAX 324)

MedDRA system organ classes	**Very common adverse reactions ≥10% of patients**	**Common adverse reactions ≥1 to <10% of patients**	**Uncommon adverse reactions ≥0.1 to <1% of patients**
Investigations	Weight decreased		Weight increased
Cardiac disorders		Arrhythmia (G3/4: 2.0%)	Myocardial ischaemia
Blood and the lymphatic system disorders	Neutropenia (G3/4: 83.5%) Anaemia (G3/4: 12.4%) Thrombocytopenia (G3/4: 4.0%) Febrile neutropenia	Febrile neutropenia*	
Nervous system disorders	Dysgeusia/Parosmia (G3/4: 0.4%) Peripheral sensory neuropathy (G3/4: 1.2%)	Dizziness (G3/4: 2.0%) Peripheral motor neuropathy (G3/4: 0.4%)	
Eye disorders		Lacrimation increased	Conjunctivitis
Ear and labyrinth disorders	Hearing impaired (G3/4: 1.2%)		
Gastrointestinal disorders	Nausea (G3/4: 13.9%) Stomatitis (G3/4: 20.7%) Vomiting (G3/4: 8.4%) Diarrhoea (G3/4: 6.8%) Oesophagitis/dysphagia /odynophagia (G3/4: 12.0%) Constipation (G3/4: 0.4%)	Dyspepsia (G3/4: 0.8%) Gastrointestinal pain/cramping (G3/4: 1.2%) Gastrointestinal haemorrhage (G3/4: 0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4: 4.0%) Pruritic rash	Dry skin desquamation	
Musculoskeletal and connective tissue disorders		Myalgia (G3/4: 0.4%)	
Metabolism and nutrition disorders	Anorexia (G3/4: 12.0%)		
Infections and infestations	Infection (G3/4: 3.6%)	Neutropenic infection	
Neoplasms benign and malignant (including cysts and polyps)		Cancer pain (G3/4: 1.2%)	
Vascular disorders			Venous disorder
General disorders and administration site conditions	Lethargy (G3/4: 4.0%) Pyrexia (G3/4: 3.6%) Fluid retention (G3/4: 1.2%) Oedema (G3/4: 1.2%)		
Immune system disorders			Hypersensitivity

* Febrile neutropenia: grade ≥2 fever concomitant with Grade 4 neutropenia requiring I.V antibiotics and/or hospitalisation. Clinically important TEAEs were determined based upon frequency, severity and clinical impact of the adverse event.

Post-marketing experience

Cardiac disorders

Rare cases of myocardial infarction have been reported.

Hypertension, hypotension, cardiac arrhythmia, congestive heart failure, atrial fibrillation, syncope, tachycardia, and ECG abnormalities has been reported.

Ventricular arrhythmia including ventricular tachycardia has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide, and may be associated with fatal outcome.

Vein disorder, venous thromboembolism and haemorrhage have been reported.

Blood and the lymphatic system disorders

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

Nervous system disorders

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

Eye disorders

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

Cases of Cystoid Macular Oedema (CMO) have been reported in patients treated with docetaxel, as well as with other taxanes.

Ear and labyrinth disorders

Rare cases of ototoxicity, impaired hearing and/or hearing loss have been reported, including cases associated with other ototoxic drugs.

Hypoacusis has been recorded.

Respiratory, thoracic and mediastinal disorders

Dyspnoea have been reported. Acute respiratory distress syndrome, interstitial pneumonia, acute pulmonary oedema, and pulmonary fibrosis have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

Gastrointestinal disorders

Rare occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, colitis ischaemic, colitis, gastrointestinal haemorrhage, and neutropenic enterocolitis have been reported. Colitis ischaemic, colitis and neutropenic enterocolitis have been reported with a fatal

outcome. Rare cases of constipation, oesophagitis, taste perversion, ileus and intestinal obstruction have been reported. Very rare cases of duodenal ulcer have been reported.

Skin and subcutaneous tissue disorders

Very rare cases of cutaneous lupus erythematous and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, have been reported with docetaxel. In some cases concomitant factors may have contributed to the development of these effects. Scleroderma-like change usually preceded by peripheral lymphedema have been reported with docetaxel. Cases of permanent alopecia have been reported.

Acute generalised exanthematous pustulosis has been reported.

Neoplasms benign and malignant (including cysts and polyps)

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

Vascular disorders

Venous thromboembolic events have rarely been reported.

General disorders and administration site conditions

Radiation recall phenomena have rarely been reported.

Dehydration and pulmonary oedema have rarely been reported.

Chest pain, diffuse pain and abdominal pain have been reported.

Fluid retention (pleural effusion, pericardial effusion, ascites), injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) has been observed at the site of previous extravasation.

Investigations

Liver function test abnormal, weight decreased, blood bilirubin increased, blood alkaline phosphatase increased, AST increased, ALT increased.

Immune system disorders

Some cases of anaphylactic shock, sometimes fatal, in patients who received premedication have been reported.

Hypersensitivity reactions such as bronchospasm and generalised rash have been reported.

Hypersensitivity reactions have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

Hepato-biliary disorders

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

Metabolism and nutrition disorders

Tumour lysis syndrome has been reported. Cases of electrolyte imbalance have been reported. Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia. Hypokalaemia, hypomagnesaemia and hypocalcaemia were observed, usually in association with gastrointestinal disorders and in particular diarrhoea.

Musculoskeletal and connective tissue disorders

Myositis has been reported.

Urogenital

Rare cases of renal insufficiency and renal failure associated with concomitant nephrotoxic drugs have been reported.

Other

Generalised or localised pain including chest pain without cardiac or respiratory involvement.

4.9 Overdose

There were a few reports of overdose. One patient received docetaxel 150 mg/m^2 and the other received docetaxel 200 mg/m^2 as a one-hour infusion. They both recovered after experiencing severe neutropenia, mild asthenia, cutaneous reactions and mild paraesthesia. 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

Pharmaco-therapeutic group: Taxanes, ATC Code: L01CD 02

Preclinical data

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

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

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

in vivo, docetaxel was synergistic with vincristine (administered at the same time), etoposide, cyclophosphamide or fluorouracil, but not with vincristine (administered 24 hours apart), cisplatin or doxorubicin.

Clinical data

Breast cancer

Docetaxel as single agent

Patients treated at 100 mg/m^2. Phase III trials

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/m^2 every 3 weeks for seven and ten cycles, respectively.

In alkylating-failure patients, docetaxel was compared to doxorubicin (75 mg/m^2 every 3 weeks), there were no significant differences in median time to progression or median survival between docetaxel (D; n = 161) and doxorubicin (DX; n = 165) on intent-to-treat and evaluable patient analyses. For the intent-to-treat analysis, without affecting overall survival time docetaxel 14.7 months vs. doxorubicin 14.3 months (D-DX diff: 0.4 months; 95% CI for diff: -1.9 to 2.7, p=0.38) or time to progression docetaxel 5.9 months vs. doxorubicin 4.9 months (D-DX diff: 1.0 month; 95% confidence interval (CI) for diff: -0.5 to 1.9, p=0.54), docetaxel increased response rate (47.8% vs. 33.3%, D-DX diff: 14.5%, 95% CI for diff: 3.9 to 25.0, 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 (n = 203) was compared to the combination of Mitomycin C and Vinblastine (MV; n = 189; 12 mg/m^2 every 6 weeks and 6 mg/m^2 every 3 weeks). For the intent-to-treat analysis, docetaxel increased response rate (30% vs. 11.6%, D-MV diff: 18.4%; 95% CI for diff: 10.6 to 26.2, p<0.0001), prolonged median time to progression (4.3 months vs. 2.5 months, D-MV diff: 1.8 months; 95% CI for diff: 1.0 to 2.4, p=0.0004) and prolonged median overall survival (11.5 months vs. 8.7 months, D-MV diff: 2.8 months; 95% CI for diff: 0.1 to 4.3, 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, multicentre, randomised 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 randomised to receive either docetaxel monotherapy 100 mg/m^2 as a 1-hour infusion or paclitaxel 175 mg/m^2 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). Efficacy results are described in the table below.

Efficacy of docetaxel versus paclitaxel in the treatment of advanced breast cancer (intent-to-treat analysis, unless specified)

Endpoint	**Docetaxel 100 mg/m^2 n=225**	**Paclitaxel 175 mg/m^2 n=224**	**p-value (unadjusted)**
Median survival (months) 95% CI	15.3 (13.3 – 18.5)	12.7 (10.5 – 14.8)	0.03

Median time to progression (weeks) 95% CI	24.6 (20 - 30.1)	15.6 (13.4 – 18.1)	<0.01
*Overall response rate (ORR) (%) 95% CI	32.0 (25.9 – 38.1)	25.0 (19.3 – 30.7)	0.10
*ORR in the evaluable population (%) 95% CI	37.0 (30.2 – 43.9)	26.0 (19.9 – 31.9)	0.01

* Primary study endpoint

The most frequent adverse events reported for docetaxel were neutropenia, febrile neutropenia, gastrointestinal disorders, neurological disorders, asthenia and fluid retention. More Grade 3/4 adverse events were observed for docetaxel monotherapy (55.4%) compared to paclitaxel (23.0%). No unexpected toxicities were reported for docetaxel.

Docetaxel in combination with doxorubicin

One large randomised Phase III study, involving 429 previously untreated patients with metastatic disease, was performed with doxorubicin (50 mg/m^2) in combination with docetaxel (75 mg/m^2) (AT arm) versus doxorubicin (60 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) (AC arm). Both regimens were administered on day 1 every 3 weeks.

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

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

In both arms, quality of life measured by the EORTC questionnaire was comparable and stable during treatment and follow-up.

Docetaxel in combination with capecitabine

Data from one open label, multicentre, randomised, controlled Phase III clinical trial supported the use of docetaxel in combination with capecitabine for treatment of 511 patients with locally advanced or metastatic breast cancer resistant to, or recurring after an anthracycline containing therapy, or relapsing during or recurring within two years of completing an anthracycline containing adjuvant therapy were enrolled. In this trial, 255 patients were randomised to treatment with docetaxel (75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks) and capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by 1-week rest period).

256 patients were randomised to treatment with docetaxel alone (100 mg/m^2 as a 1-hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel + capecitabine combination arm (p=0.0119). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (docetaxel + capecitabine) vs. 29.7% (docetaxel alone); p = 0.0058. Time to progressive disease

was superior in the docetaxel + capecitabine combination arm (p=0.0001). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone) and hazard ratio was 0.643.

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/m^2 compared to Best Supportive Care (BSC). 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/m^2 compared to those with BSC.

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

Docetaxel in combination with platinum agents in chemotherapy-naïve patients

In a Phase III trial, 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, 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.

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

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

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

Secondary end-points included change of pain, global rating of quality of life by EuroQoL-5D, Lung Cancer Symptom Scale, and changes in Karnofsky performance status. Results on these end-points were supportive of the primary end-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 randomised multicentre Phase III trial. A total of 1006 patients with KPS ≥60 were randomised 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 (p=0.0094). 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 summarised in the following table:

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

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

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

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

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

Gastric adenocarcinoma

A multicentre, open-label, randomised trial, was conducted to evaluate the safety and efficacy of docetaxel for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for metastatic disease. A total of 445 patients with KPS>70 were treated with either docetaxel (T) (75 mg/m^2 on day 1) in combination with cisplatin (C) (75 mg/m^2 on day 1) and 5-fluorouracil (F) (750 mg/m^2 per day for 5 days) or cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1,000 mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TPF arm and 4 weeks for the CF

arm. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TPF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p=0.0004) in favour of the TPF arm. Overall survival was also significantly longer (p=0.0201) in favour of the TPF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarised in the following table:

Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

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

* Unstratified log-rank test

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

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

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

<u>*Head and neck cancer*</u>

Induction chemotherapy followed by radiotherapy (TAX 323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a Phase III, multicentre, open-label, randomised trial (TAX 323). In this study, 358 previously untreated patients with inoperable locally advanced stage III/IV SCCHN, and WHO performance status 0 or 1, were randomised to one of two treatment arms, received either docetaxel 75 mg/m^2 followed by cisplatin 75 mg/m^2 on day 1, followed by 5-fluorouracil 750 mg/m^2 per day as a continuous infusion for 5 days (TPF). The cycles were repeated every three weeks for four cycles. Patients on the comparator arm received cisplatin 100 mg/m^2 on day 1, followed by 5-fluorouracil 1,000 mg/m^2 (PF) per day as a continuous infusion for 5 days. These regimens were administered every three weeks for 4 cycles in case at least a minor response (≥25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (PF/RT) for 7 weeks. Locoregional therapy with radiation was delivered to approximately 77% of the patients either with a conventional fraction (1.8 Gy-2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy were used in approximately 23% of

patients (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week). A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy. Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p=0.0042 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow-up time of 33.7 months. Median overall survival (OS) was also significantly longer in favour of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, p=0.0128. Patients with tumours of the nasopharynx and the nasal/paranasal cavities were excluded from this study. Efficacy results are presented in the table below:

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

Endpoint	**Docetaxel+ Cis+5-FU n=177**	**Cis+5-FU n=181**
Median progression free survival (months) (95% CI)	11.4 (10.1-14.0)	8.3 (7.4-9.1)
Adjusted hazard ratio (95% CI) *p-value	0.70 (0.55-0.89) 0.0042	
Median survival (months) (95% CI)	18.6 (15.7-24.0)	14.5 (11.6-18.7)
Hazard ratio (95% CI) **p-value	0.72 (0.56-0.93) 0.0128	
Best overall response to chemotherapy (%) (95% CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response to study treatment [chemotherapy +/- radiotherapy] (%) (95% CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	
Median duration of response to chemotherapy ± radiotherapy (months) (95% CI)	n=128 15.7 (13.4-24.6)	n=106 11.7 (10.2-17.4)
Hazard ratio (95% CI) **p-value	0.72 (0.52-0.99) 0.0457	

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

Quality of life parameters

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

Clinical benefit parameters

The performance status scale, for head and neck (PSS-HN) subscales designed to measure understandability of speech, ability to eat in public, and normalcy of diet, was significantly in favour of TPF as compared to PF.

Median time to first deterioration of WHO performance status was significantly (p=0.0158) longer in the TPF arm (13.7 months; 95% CI: 10.7 to 21.0 months) compared to PF (8.3 months; 95% CI: 7.3 to 9.6 months). However, no significant difference in WHO performance status was apparent between the

two arms (odds ratio = 0.96, 95% CI: 0.66 to 1.41). There was no difference in pain intensity in patients treated with TPF or PF.

Induction chemotherapy followed by chemoradiotherapy (TAX 324)

The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a randomised, multicentre open-label, Phase III, trial (TAX 324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomised to one of two arms. The study population comprised patients with technically unresectable disease, patients with low probability of surgical cure and patients aiming at organ preservation. The efficacy and safety evaluation solely addressed survival endpoints and the success of organ preservation was not formally addressed. Patients on the docetaxel arm received docetaxel (T) 75 mg/m^2 by intravenous infusion on day 1 followed by cisplatin (P) 100 mg/m^2 administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of 5-fluorouracil (F) 1,000 mg/m^2/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100 mg/m^2 as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of 5-fluorouracil (F) 1,000 mg/m^2/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).

Patients in both treatment arms were to receive 7 weeks of CRT following induction chemotherapy with a minimum interval of 3 weeks and no later than 8 weeks after start of the last cycle (day 22 to day 56 of last cycle). During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour intravenous infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks, for a total dose of 70-72 Gy). Surgery on the primary site of disease and/or neck could be considered at anytime following completion of CRT. All patients on the docetaxel-containing arm of the study received prophylactic antibiotics. The primary efficacy endpoint in this study, overall survival (OS) was significantly longer (log-rank test, p = 0.0058) with the docetaxel-containing regimen compared to PF (median OS: 70.6 versus 30.1 months respectively), with a 30% risk reduction in mortality compared to PF (hazard ratio (HR) = 0.70, 95% confidence interval (CI) = 0.54-0.90) with an overall median follow up time of 41.9 months. The secondary endpoint, PFS, demonstrated a 29% risk reduction of progression or death and a 22-month improvement in median PFS (35.5 months for TPF and 13.1 for PF). This was also statistically significant with an HR of 0.71; 95% CI 0.56-0.90; log-rank test p = 0.004. Efficacy results are presented in the table below:

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

Endpoint	**Docetaxel + Cis + 5-FU n = 255**	**Cis + 5-FU n = 246**
Median overall survival (months) (95% CI)	70.6 (49.0-NA)	30.1 (20.9-51.5)
Hazard ratio (95% CI) *p-value	0.70 (0.54-0.90) 0.0058	
Median PFS (months) (95% CI)	35.5 (19.3-NA)	13.1 10.6-20.2)
Hazard ratio (95% CI) **p-value	0.71 (0.56-0.90) 0.004	
Best overall response (CR + PR) to chemotherapy (%) (95% CI)	71.8 (65.8-77.2)	64.2 (57.9-70.2)
***p-value	0.070	

Best overall response (CR + PR) to study treatment [chemotherapy +/- chemoradiotherapy] (%) (95% CI)	76.5 (70.8-81.5)	71.5 (65.5-77.1)
***p-value	0.209	

A Hazard ratio of less than 1 favours docetaxel + cisplatin + 5-fluorouracil.
* Unadjusted log-rank test
** Unadjusted log-rank test, not adjusted for multiple comparisons
*** Chi square test, not adjusted for multiple comparisons
NA-not applicable

5.2 Pharmacokinetic properties

Absorption

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 area under the curve (AUC) of 4.6 hour. μg/mL.

Distribution

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5-115 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 minutes, 36 minutes and 11.1 hours, respectively.

The initial rapid decline represents distribution to the peripheral compartments and the late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100 mg/m^2 dose given as a one-hour infusion, mean value for steady-state volume of distribution was 113 L. Docetaxel is more than 95% bound to plasma proteins.

Metabolism and excretion

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 (60% of the administered dose) 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 drug.

Following the administration of a 100 mg/m^2 dose given as a one-hour infusion, the mean value for total body clearance was 21 L/hour/m^2. Inter individual variation in total body clearance was approximately 50%.

An additional study assessing the pharmacokinetics of docetaxel at similar doses (75–100 mg/m^2) in patients, but over a longer time interval (over 22 days) found a longer mean terminal elimination half-life between 91 and 120 hours.

Effect of age, sex and organ impairment

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

Drug-drug interaction

Dexamethasone did not affect protein binding of docetaxel.

The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of docetaxel was observed.

When used in combination, docetaxel does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite).

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

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

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

5.3 Preclinical safety data

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

Docetaxel has been shown to be both embryotoxic and fetotoxic in rabbits and rats, and to reduce fertility in rats.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (anhydrous)
Ethanol anhydrous
Macrogol 300
Polysorbate 80

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

Do not use later than the date of expiry shown on the packaging.

Shelf life after dilution

After dilution in 0.9% sodium chloride or 5% glucose chemical and physical in-use stability has been demonstrated for 4 hours when stored below 25°C. From a microbiological point of view, the infusion preparation should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C.

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

2 mL or 8 mL in a vial (Type I clear glass with or without ONCO-TAIN™ overwrap) with chlorobutyl elastomeric closures and aluminium seals with plastic flip-off cap.

Pack size: 1 x 2 mL or 1 x 8 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Hospira Docetaxel Concentrate for Solution for Infusion is an antineoplastic agent and, as with other potentially toxic agents, caution should be exercised during handling and preparing solutions of Hospira Docetaxel Concentrate for Solution for Infusion.

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

Guidelines for the safe handling and disposal of antineoplastic agents preparation

Local guidelines on safe preparation and handling should be consulted.

Cytotoxic agents should only be prepared and handled by personnel trained in the safe handling of such preparations. Pregnant personnel should not handle cytotoxic agents.

All personnel involved with handling cytotoxic agents should be adequately protected with appropriate personal protective equipment, including protective disposable gloves, eye shield, mask and long-sleeved gown. Preparation and manipulation of solutions should be performed in a designated handling area.

Contamination

In the event of skin contact, thoroughly wash the affected area with soap and water, taking care not to abrade the skin. A bland cream may be used to treat transient stinging of the skin. In the event of contact with the eyes, irrigate with copious amounts of water or sodium chloride 0.9%. Seek medical evaluation.

In the event of spillage, trained personnel wearing appropriate personal protective equipment should remove the maximum amount of material by use of a cytotoxic drug spill kit or designated absorbent

materials. The area should be rinsed with copious amounts of water. All contaminated cleaning materials should be disposed of as described below.

Disposal

All contaminated waste materials (including sharps, containers, absorbent materials, unused solutions, etc.) should be placed in a designated sealed and labelled impervious waste disposal bag or rigid waste container, and incinerated in accordance with local procedures for destruction of hazardous waste.

Instructions for preparation

Refer to Section 6.3 Shelf life.

Inspect visually prior to use. Only clear solutions without visible particles should be used. **Must be diluted before use.**

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

Inject the required volume into a 250 mL infusion bag or bottle containing either:

- Sodium Chloride 9 mg/mL (0.9%)
- Glucose 50 mg/mL (5%)

If a dose greater than 185 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.

Compatibility

It is not recommended to mix docetaxel with other drugs.

Administration

For instructions on administration see Section 4.2.

7 NAME AND ADDRESS OF PRODUCT OWNER

Hospira Australia Pty Ltd.
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Australia

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