Public Assessment Report

Decentralised Procedure

Docetaxel Actavis 20mg/0.5ml concentrate and solvent for solution for infusion
(docetaxel)

Docetaxel Actavis 80mg/2ml concentrate and solvent for solution for infusion
(docetaxel)

Procedure No: UK/H/1917/001-002/DC
UK Licence No: PL 30306/0143-4

Actavis Group PTC ehf
LAY SUMMARY

On 22 June 2010, the MHRA granted Actavis Group PTC ehf Marketing Authorisations for the medicinal products Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion (PL 30306/0143-4; UK/H/1917/001-002/DC). These are prescription-only medicines (POM) intended for the treatment of breast cancer, special forms of lung cancer (non-small cell lung cancer), prostate cancer, gastric cancer, or head and neck cancer.

Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion contain the active ingredient docetaxel, a substance derived from the needles of yew trees which belongs to a group of anti-cancer medicines known as taxoids.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion outweigh the risks, hence Marketing Authorisations have been granted.
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# Module 1

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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substances</strong></td>
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<td><strong>Form</strong></td>
<td>Concentrate and solvent for solution for infusion</td>
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<tr>
<td><strong>Strength</strong></td>
<td>20mg/0.5ml and 80mg/2ml</td>
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<td><strong>MA Holder</strong></td>
<td>Actavis Group PTC ehf., Reykjavikurvegur 76-78, 220 Hafnarfjörður, Iceland</td>
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<td><strong>Reference Member State (RMS)</strong></td>
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</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Belgium, Cyprus, Greece, Iceland, Lithuania, Latvia, Malta, Romania and Slovenia</td>
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<td>UK/H/1917/001-002/DC</td>
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<td><strong>Timetable</strong></td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Docetaxel Actavis 20mg/0.5ml concentrate and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single dose vial contains docetaxel 20mg/0.5ml.
Each single dose vial contains 40mg/ml of docetaxel.
Each single dose vial contains 10mg/ml of docetaxel after reconstitution with the accompanying solvent.

Excipients:
Each single dose 20mg/0.5ml vial of concentrate contains 50mg ethanol absolute.
Each single dose vial of solvent contains 9.53% (w/w) ethanol absolute.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate and solvent for solution for infusion.
The concentrate is a clear, oily, yellow solution.
The solvent is a clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Breast cancer
Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

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

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

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

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

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

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

Prostate cancer
Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.
Gastric Adenocarcinoma
Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.

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

4.2 Posology and method of administration
The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy. After reconstitution of the concentrate vial with the appropriate solvent, the premix solution should be homogenous and clear (foaming is normal even after 3 minutes due to the presence of polysorbate 80 in the formulation). (See section 6.6 for instructions on the dilution of the product before administration).

Recommended dosage
For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg 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 hematological toxicities.

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

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

Breast cancer
In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel is 75mg/m² administered 1-hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² every 3 weeks for 6 cycles (see also Dosage adjustments during treatment).

For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dosage of docetaxel is 100mg/m² in monotherapy. In first-line treatment, docetaxel 75mg/m² is given in combination therapy with doxorubicin (50mg/m²).

In combination with trastuzumab the recommended dose of docetaxel is 100mg/m² every three weeks, with trastuzumab administered weekly. In the pivotal trial the initial docetaxel infusion was started the day following the first dose of trastuzumab. The subsequent docetaxel doses were administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. For trastuzumab dosage and administration, see trastuzumab summary of product characteristics.

In combination with capecitabine, the recommended dose of docetaxel is 75mg/m² every three weeks, combined with capecitabine at 1250mg/m² 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 75mg/m² immediately followed by cisplatin 75mg/m² over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dosage is 75mg/m² as a single agent.

Prostate cancer
The recommended dose of docetaxel is 75mg/m². Prednisone or prednisolone 5mg orally twice daily is administered continuously (see section 5.1).

Gastric adenocarcinoma
The recommended dose of docetaxel is 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m² per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion.
Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of hematological toxicities (See also 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 hematological toxicities. All patients on the docetaxel-containing arm of the TAX 323 and TAX 324 studies, received prophylactic antibiotics.

- **Induction chemotherapy followed by radiotherapy (TAX 323)**
  For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75mg/m² as a 1 hour infusion followed by cisplatin 75mg/m² over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750mg/m² 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 75mg/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100mg/m² administered as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000mg/m²/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.

**Dosage adjustments during treatment**

**General**

Docetaxel should be administered when the neutrophil count is ≥ 1,500cells/mm³. In patients who experienced either febrile neutropenia, neutrophil < 500cells/mm³ 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 100mg/m² to 75mg/m² and/or from 75 to 60mg/m². If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued.

**Adjuvant therapy for breast cancer**

In the pivotal trial in patients who received adjuvant therapy for breast cancer and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg, day 4 to 11) in all subsequent cycles. Patients who continued to experience this reaction should remain on G-CSF and have their docetaxel dose reduced to 60mg/m².

However, in clinical practice neutropenia could occur earlier. Thus the use of G-CSF should be considered function of the neutropenic risk of the patient and current recommendations. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m².

**In combination with cisplatin**

For patients who are dosed initially at docetaxel 75mg/m² in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 25000cells/mm³, or in patients who experience febrile neutropenia, or in patients with serious non-hematologic toxicities, the docetaxel dosage in subsequent cycles should be reduced to 65mg/m². 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 55mg/m².
• For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose.

For trastuzumab dose modifications, see trastuzumab summary of product characteristics

**In combination with cisplatin and 5-fluorouracil:**
If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60mg/m². If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45mg/m². In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60mg/m². Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. 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):

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea grade 3</td>
<td>First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.</td>
</tr>
<tr>
<td>Diarrhoea grade 4</td>
<td>First episode: reduce docetaxel and 5-FU doses by 20%. Second episode: discontinue treatment.</td>
</tr>
<tr>
<td>Stomatitis/mucositis grade 3</td>
<td>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%.</td>
</tr>
<tr>
<td>Stomatitis/mucositis grade 4</td>
<td>First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%.</td>
</tr>
</tbody>
</table>

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

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

**Special populations**

**Patients with hepatic impairment**
Based on pharmacokinetic data with docetaxel at 100mg/m² as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75mg/m² (see sections 4.4 and 5.2). For those patients with serum bilirubin > ULN and/or ALT and AST > 3.5 times the ULN associated with alkaline phosphatase > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.
In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical trial excluded patients with ALT and/or AST > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin > 1 x ULN; for these patients, no dose-reductions can be recommended and docetaxel should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by docetaxel in combination 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
- Hypersensitivity to the active substance or to any of the excipients.
- Docetaxel must not be used in patients with baseline neutrophil count of < 1,500 cells/mm³.
- Docetaxel must not be used in patients with severe liver impairment since there is no data available (see sections 4.2 and 4.4).

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

### 4.4 Special warnings and precautions for use
For breast and non-small cell lung cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg 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 8mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see section 4.2).

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

In the case of severe neutropenia (< 500 cells/mm³ for seven days or more) during a course of docetaxel therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended (see section 4.2).

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

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

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

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

#### Patients with liver impairment
In patients treated with docetaxel at 100mg/m² as single agent who have serum transaminase levels (ALT and/or AST) greater than 1.5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of docetaxel...
in those patients with elevated liver function test (LFTs) is 75mg/m² and LFTs should be measured at base line and before each cycle (see section 4.2).

For patients with serum bilirubin levels > ULN and/or ALT and AST > 3.5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

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

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

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

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

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

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

Additional cautions for use in adjuvant treatment of breast cancer

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

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

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

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

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

Elderly
There are no data available in patients > 70 years of age on docetaxel use in combination with doxorubicin and cyclophosphamide.
Of the 333 patients treated with docetaxel every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with docetaxel every three weeks, the incidence of related nail changes occurred at a rate ≥ 10% higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, diarrhea, anorexia, and peripheral edema occurred at rates ≥ 10% higher in patients who were 75 years of age or greater versus less than 65 years.

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

**Ethanol**

Docetaxel contains 100mg of ethanol absolute per ml concentrate. The solvent contains 9.53% (w/w) ethanol absolute. This may be harmful in patients suffering from alcoholism. The ethanol content of this medicinal product should be taken into account when used children or in high-risk groups such as patients with liver disease, or epilepsy.

**4.5 Interaction with other medicinal products and other forms of interaction**

There have been no formal clinical studies to evaluate the interactions of docetaxel with other medicinal products.

In *vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporin, terfenadine, ketoconazole, erythromycin and troleandomycin. 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.

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

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

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

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

The ethanol content of this medicinal product may alter the effects of other medicines.

**4.6 Pregnancy and lactation**

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

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

An effective method of contraception should be used during treatment.

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

**Lactation:**

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

**4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. The ethanol content of this medicinal product may impair the ability to drive or use machines.

**4.8 Undesirable effects**

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

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

These reactions were described using the NCI Common Toxicity Criteria (grade 3 = G3; 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).

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/mm³) was 7 days), anemia, alopecia, nausea, vomiting, stomatitis, diarrhea and asthenia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

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

For combination with capecitabine, the most frequent treatment-related undesirable effects (≥5%) reported in a phase III trial in breast cancer patients failing anthracycline treatment are presented (see capecitabine summary of product characteristics).
The following adverse reactions are frequently observed with docetaxel:

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

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

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

**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 generalized rash/erythema (see section 4.4).

**Docetaxel 100g/m² single agent:**

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<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td>G3/4 Blood bilirubin increased (&lt;5%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>G3/4 Blood alkaline phosphatase increased (&lt;4%);</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>G3/4 AST increased (&lt;3%);</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>G3/4 ALT increased (&lt;2%);</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Neutropenia (G4: 76.4%);</td>
<td>Thrombocytopenia (G4: 0.2%);</td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Anaemia (G3/4: 8.9%); Febrile neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3: 4.1%);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral motor neuropathy (G3/4: 4%);</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysgeusia (severe 0.07%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea (severe 2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis (G3/4: 5.3%);</td>
<td>Constipation (severe 0.2%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhoea (G3/4: 4%);</td>
<td>Abdominal pain (severe 1%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea (G3/4: 4%);</td>
<td>Gastrointestinal Haemorrhage (severe 0.3%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting (G3/4: 3%)</td>
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<td></td>
</tr>
</tbody>
</table>

13
**MedDRA System Organ classes**

<table>
<thead>
<tr>
<th>Very common adverse reactions</th>
<th>Common adverse reactions</th>
<th>Uncommon adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥ 1/10</strong></td>
<td><strong>≥ 1/100, &lt; 1/10</strong></td>
<td><strong>≥ 1/1000, &lt; 1/100</strong></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Alopecia; Skin reaction (G3/4: 5.9%); Nail disorders (severe 2.6%)</td>
<td>Arthralgia</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Myalgia (severe 1.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)</td>
<td>Infection associated with G4 neutropenia (G3/4: 4.6%)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Hypotension; Hypertension; Haemorrhage</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Fluid retention (severe: 6.5%); Asthenia (severe 11.2%); Pain</td>
<td>Infusion site reaction; Non-cardiac chest pain (severe)</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Hypersensitivity (G3/4: 5.3%)</td>
<td></td>
</tr>
</tbody>
</table>

**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 100mg/m² as single agent. The events were spontaneously reversible within 3 months.

**Skin and subcutaneous tissue disorders**

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

**General disorders and administration site conditions**

The median cumulative dose to treatment discontinuation was more than 1,000mg/m² 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: 818.9mg/m²) in patients with premedication compared with patients without premedication (median cumulative dose: 489.7mg/m²); however, it has been reported in some patients during the early courses of therapy.

**Docetaxel 75mg/m² single agent:**

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions</th>
<th>Common adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥ 1/10</strong></td>
<td>G3/4 Blood bilirubin Increased (&lt;2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Arrhythmia (no severe);</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td>Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Peripheral sensory neuropathy (G3/4: 0.8%)</td>
<td>Peripheral motor neuropathy (G3/4: 2.5%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhoea (G3/4: 1.7%)</td>
<td>Constipation</td>
</tr>
<tr>
<td>MedDRA System Organ classes</td>
<td>Very common adverse reactions</td>
<td>Common adverse reactions</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Skin reaction (G3/4: 0.8%)</td>
<td>Nail disorders (severe 0.8%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infections (G3/4: 5%)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (severe 12.4%); Fluid retention (severe 0.8%); Pain</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity (no severe)</td>
</tr>
</tbody>
</table>

Docetaxel 75mg/m² in combination with doxorubicin:

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions</th>
<th>Common adverse reactions</th>
<th>Uncommon adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td>G3/4 Blood bilirubin increased (&lt;2.5%); G3/4 Blood alkaline phosphatase increased (&lt;2.5%);</td>
<td>G3/4 AST increased (&lt;1%); G3/4 ALT increased (&lt;1%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure; Arrhythmia (no severe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3: 0.4%)</td>
<td>Peripheral motor neuropathy (G3/4: 0.4%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhoea (G3/4: 6.2%); Vomiting (G3/4: 5%); Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Nail disorders (severe 0.4%); Skin reaction (no severe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4: 7.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (severe 8.1%); Fluid retention (severe 1.2%); Pain</td>
<td></td>
<td>Infusion site reaction</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity (G3/4: 1.2%)</td>
<td></td>
</tr>
</tbody>
</table>
**Docetaxel 75mg/m² in combination with cisplatin:**

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased (1.3%)</td>
<td>G3/4 AST increased (0.5%); G3/4 Blood alkaline Phosphatase increased (0.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4:0.5%)</td>
<td>Febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmia (G3/4: 0.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%)</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Myalgia (severe 0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Alopecia; Nail disorders (severe 0.7%); Skin reaction (G3/4:0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Infection (G3/4: 5.7%)</td>
<td>Hypotension (G3/4:0.7%)</td>
<td>Infusion site reaction; Pain</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Asthenia (severe 9.9%); Fluid retention (severe 0.7%); Fever (G3/4:1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infecions and infestations</td>
<td>Hyperesensitivity (G3/4: 2.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Docetaxel 100mg/m² in combination with trastuzumab:**

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure</td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G3/4: 32%); Febrile neutropenia (includes neutropenia associated with fever and antibiotic use) or neutropenic sepsis</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paresthesia; Headache; Dyseusia; Hypoaesthesia</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased; Conjunctivitis</td>
<td></td>
</tr>
</tbody>
</table>
MedDRA System Organ classes | Very common adverse reactions ≥ 1/10 | Common adverse reactions ≥ 1/100, < 1/10 |
---|---|---|
Respiratory, thoracic and mediastinal disorders | Epistaxis; Pharyngolaryngeal pain; Nasopharyngitis; Dyspnoea; Cough; Rhinorrhoea |  |
Gastrointestinal disorders | Nausea; Diarrhoea; Vomiting; Constipation; Stomatitis; Dyspepsia; Abdominal pain |  |
Skin and subcutaneous tissue disorders | Alopecia; Erythema; Rash; Nail disorders |  |
Musculoskeletal and connective tissue disorders | Myalgia; Arthralgia; Pain in extremity; Bone pain; Back pain |  |
Metabolism and nutrition disorders | Anorexia |  |
Vascular disorders |  | Lethargy |
General disorders and administration site conditions | Asthenia; Oedema peripheral; Pyrexia; Fatigue; Mucosal inflammation; Pain; Influenza like illness; Chest pain; Chills |  |
Psychiatric disorders | Insomnia |  |

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

Blood and the lymphatic system disorders
Very common: Haematological toxicity was increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m² is known to result in neutropenia in 97% of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

Docetaxel 75mg/m² in combination with capecitabine:

| MedDRA System Organ classes | Very common adverse reactions ≥ 1/10 | Common adverse reactions ≥ 1/100, < 1/10 |
---|---|---|
Investigations | Weight decreased; G3/4 Blood bilirubin increased (9%) | Thrombocytopenia (G3/4: 3%) |
Blood and the lymphatic system disorders | Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%) |  |
Nervous system disorders | Dysgeusia (G3/4: <1%); Parasthesia (G3/4: <1%) | Dizziness; Headache (G3/4: <1%); Neuropathy peripheral |
Eye disorders | Lacrimation increased |  |
Respiratory, thoracic and mediastinal disorders | Pharyngolaryngeal pain (G3/4: 2%) | Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%) |
Gastrointestinal disorders | Stomatitis (G3/4: 18%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4: 2%); Dyspepsia | Abdominal pain upper; Dry mouth |
Skin and subcutaneous tissue disorders | Hand-foot syndrome (G3/4: 24%); Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%) | Dermatitis; Rash erythematous (G3/4: <1%); Nail discolouration; Onycholysis (G3/4: 1%) |
Musculoskeletal and connective tissue disorders | Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%) | Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%); |
MedDRA System Organ classes | Very common adverse reactions | Common adverse reactions
--- | --- | ---
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 75mg/m² in combination with prednisone or prednisolone:**

| MedDRA System Organ classes | Very common adverse reactions | Common adverse reactions |
--- | --- | ---
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%);
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 | Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%) | Epistaxis (G3/4: 0%);
Gastrointestinal disorders | | Dyspnoea (G3/4: 0.6%);
Skin and subcutaneous tissue disorders | Alopecia; Nail disorders (no severe) | Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue disorders | | Arthralgia (G3/4: 0.3%);
Metabolism and nutrition disorders | Anorexia (G3/4: 0.6%) | Myalgia (G3/4: 0.3%)
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 75mg/m² in combination with doxorubicin and cyclophosphamide:**

| MedDRA System Organ classes | Very common adverse reactions | Common adverse reactions | Uncommon adverse reactions |
--- | --- | --- | ---
Investigations | Weight increased or decreased (G3/4: 0.3%) | | |
Cardiac disorders | | Arrhythmia (G3/4: 0.1%); Congestive heart failure |
Blood and the lymphatic system disorders | Anaemia (G3/4: 4.3%); Neutropenia (G3/4: 65.5%); Thrombocytopenia (G3/4: 2.0%); Febrile neutropenia | |
<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)</td>
<td>Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebella (G3/4: 0.1%)</td>
<td>Syncope (G3/4: 0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough (G3/4: 0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 5.1%); Stomatitis (G3/4: 7.1%); Vomiting (G3/4: 4.3%); Diarrhoea (G3/4: 3.2%); Constipation (G3/4: 0.4%)</td>
<td>Abdominal pain (G3/4:0.5%)</td>
<td>Colitis/enteritis/large intestine perforation</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Skin toxicity (G3/4: 0.7%); Nail disorders (G3/4: 0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders.</td>
<td>Myalgia (G3/4: 0.8%); Arthralgia (G3/4:0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4: 2.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4: 3.2%); Neutropenic infection. There were no septic deaths.</td>
<td>Hypotension (G3/4: 0%)</td>
<td>Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasodilatation (G3/4: 0.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (G3/4: 11%); Fever (G3/4: 1.2%); Oedema peripheral (G3/4: 0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4: 1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Amenorrhoea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Nervous system disorders**
Peripheral sensory neuropathy was observed to be ongoing at the median follow-up time of 55 months in 9 patients out of the 73 patients with peripheral sensory neuropathy at the end of the chemotherapy.
**Skin and subcutaneous tissue disorders**
Alopecia was observed to be ongoing at the median follow-up time of 55 months in 22 patients out of the 687 patients with alopecia at the end of the chemotherapy.

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

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

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

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Arrhythmia (G3/4: 1.0%).</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Anaemia (G3/4: 20.9%); Neutropenia (G3/4: 83.2%); Thrombocytopenia (G3/4:8.8%); Febrile neutropenia.</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3/4: 8.7%).</td>
<td>Dizziness (G3/4: 2.3%); Peripheral motor neuropathy (G3/4: 1.3%).</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Lacrimation increased (G3/4: 0%).</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td>Hearing impaired (G3/4: 0%).</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Diarrhoea (G3/4: 19.7%); Nausea (G3/4: 16%); Stomatitis (G3/4: 23.7%); Vomiting (G3/4: 14.3%).</td>
<td>Constipation (G3/4: 1.0 %); Gastrointestinal pain (G3/4: 1.0%); Oesophagitis/dysphagia/odynophagia (G3/4: 0.7%).</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia (G3/4: 4.0%).</td>
<td>Rash pruritus (G3/4: 0.7%); Nail disorders (G3/4: 0.7%); Skin exfoliation (G3/4: 0%).</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4: 11.7%).</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Neutropenic infection; Infection (G3/4: 11.7%).</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Lethargy (G3/4: 19.0%); Fever (G3/4: 2.3%); Fluid retention (severe/lifethreatening: 1%).</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4:1.7).</td>
<td></td>
</tr>
</tbody>
</table>

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

Docetaxel 75mg/m² in combination with cisplatin and 5-fluorouracil for Head and Neck cancer:
- Induction chemotherapy followed by radiotherapy (TAX 323)
<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G3/4:76.3%) Anemia (G3/4:9.2) Thrombocytopenia (G3/4:5.2%)</td>
<td>Febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysequisia/Parosmia Peripheral sensory neuropathy (G3/4:0.6%)</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased Conjunctivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hearing impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4:0.6%) Stomatitis (G3/4:4.0%) Diarrhoea (G3/4:2.9%) Vomiting (G3/4:0.6%)</td>
<td>Constipation Esophagitis/ dysphagia/ odynophagia (G3/4:0.6%) Abdominal pain Dyspepsia Gastrointestinal haemorrhage (G3/4:0.6%)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia (G3/4:10.9%). Rash pruritic Dry skin Skin exfoliative (G3/4:0.6%)</td>
<td></td>
<td>Myalgia (G3/4:0.6%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4:0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4:4.3%) Neutropenic infection</td>
<td>Cancer pain (G3/4:0.6%)</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
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<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>Venous disorder (G3/4:0.6%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Lethargy (G3/4:3.4%) Pyrexia (G3/4:0.6%) Fluid retention Oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity (no severe)</td>
</tr>
</tbody>
</table>

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td></td>
<td>Weight increased</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Arrhythmia (G3/4:2.0%)</td>
<td>Ischemia myocardial</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G3/4:83.5%) Anemia (G3/4:12.4%) Thrombocytopenia (G3/4:4.0%) Febrile neutropenia</td>
<td></td>
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</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysequisia/Parosmia (G3/4:0.4%); Peripheral sensory neuropathy (G3/4:1.2%)</td>
<td>Dizziness (G3/4:2.0%); Peripheral motor neuropathy (G3/4:0.4%)</td>
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</tbody>
</table>
### MedDRA System Organ classes

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</th>
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<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
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<td><strong>Ear and labyrinth disorders</strong></td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
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<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders.</strong></td>
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<td><strong>Metabolism and nutrition disorders</strong></td>
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<tr>
<td><strong>Infections and infestations</strong></td>
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<tr>
<td><strong>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</strong></td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
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<tr>
<td><strong>Immune system disorders</strong></td>
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</tbody>
</table>

### MedDRA System Organ classes

Post-Marketing Experience:

**Cardiac disorders**
Rare cases of myocardial infarction have been reported.

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

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

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

**Respiratory, thoracic and mediastinal disorders**
Acute respiratory distress syndrome, interstitial pneumonia and pulmonary fibrosis have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.
**Gastrointestinal disorders**
Rare occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, colitis ischaemic, colitis and neutropenic enterocolitis have been reported. Rare cases of ileus and intestinal obstruction have been reported.

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

**Neoplasms benign, malignant and unspecified (incl 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. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension. Dehydration and pulmonary oedema have rarely been reported.

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

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

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Antineoplastic agents, ATC Code: L01CD 02

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

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

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

Breast cancer

Docetaxel in combination with doxorubicin and cyclophosphamide: adjuvant therapy

Data from a multicenter open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with operable node-positive breast cancer and KPS $\geq 80\%$, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomized to receive either docetaxel 75mg/m² administered 1-hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² (TAC arm), or doxorubicin 50mg/m² followed by fluorouracil 500mg/m² and cyclophosphamide 500mg/m² (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1-hour infusion, all other drugs were given as IV bolus on day one. G-CSF was administered as secondary prophylaxis to patients who experienced complicated neutropenia (febrile neutropenia, prolonged neutropenia, or infection). Patients on the TAC arm received antibiotic prophylaxis with ciprofloxacin 500mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive estrogen and/or progesterone receptors received tamoxifen 20mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received TAC and 72% of patients who received FAC.

An interim analysis was performed with a median follow up of 55 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 5 years was reduced in patients receiving TAC compared to those who received FAC (25% versus 32%, respectively) i.e. an absolute risk reduction by 7% ($p=0.001$). Overall survival at 5 years was also significantly increased with TAC compared to FAC (87% versus 81%, respectively) i.e. an absolute reduction of the risk of death by 6% ($p=0.008$). TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed:

<table>
<thead>
<tr>
<th>Patient subset</th>
<th>Number of patients</th>
<th>Hazard ratio*</th>
<th>95% CI</th>
<th>$P=^*$</th>
<th>Hazard ratio*</th>
<th>95% CI</th>
<th>$P=^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of positive nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>745</td>
<td>0.72</td>
<td>0.59-0.88</td>
<td>0.001</td>
<td>0.70</td>
<td>0.53-0.91</td>
<td>0.008</td>
</tr>
<tr>
<td>1-3</td>
<td>467</td>
<td>0.61</td>
<td>0.46-0.82</td>
<td>0.0009</td>
<td>0.45</td>
<td>0.29-0.70</td>
<td>0.0002</td>
</tr>
<tr>
<td>4+</td>
<td>278</td>
<td>0.83</td>
<td>0.63-1.08</td>
<td>0.17</td>
<td>0.94</td>
<td>0.66-1.33</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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

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

Docetaxel as single agent

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

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

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

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

An open-label, multicenter, randomized phase III study was conducted to compare docetaxel monotherapy and paclitaxel in the treatment of advanced breast cancer in patients whose previous therapy should have included an anthracycline. A total of 449 patients were randomized to receive either docetaxel monotherapy 100mg/m² as a 1 hour infusion or paclitaxel 175mg/m² as a 3 hour infusion. Both regimens were administered every 3 weeks.

Without affecting the primary endpoint, overall response rate (32% vs 25%, p=0.10), docetaxel prolonged median time to progression (24.6 weeks vs 15.6 weeks; p < 0.01) and median survival (15.3 months vs 12.7 months; p=0.03).

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

**Docetaxel in combination with doxorubicin**

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

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

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

**Docetaxel in combination with trastuzumab**

Docetaxel in combination with trastuzumab was studied for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2, and who previously had not received chemotherapy for metastatic disease. One hundred eighty six patients were randomized to receive docetaxel (100mg/m²) with or without trastuzumab; 60% of patients received prior anthracycline-based adjuvant chemotherapy. Docetaxel plus trastuzumab was efficacious in patients whether or not they had received prior adjuvant anthracyclines. The main test method used to determine HER2 positivity in this pivotal trial was immunohistochemistry (IHC). A minority of patients were tested using fluorescence in-situ hybridization (FISH). In this trial, 87% of patients had disease that was IHC 3+, and 95% of patients entered had disease that was IHC 3+ and/or FISH positive. Efficacy results are summarized in the following table:
Parameter | Docetaxel plus trastuzumab | Docetaxel
n=92 | n=94
---|---|---
Response rate (95% CI) | 61\% (50-71) | 34\% (25-45)
Median Duration of response (months) (95% CI) | 11.4 (9.2-15.0) | 5.1 (4.4-6.2)
Median TTP (months) (95% CI) | 10.6 (7.6-12.9) | 5.7 (5.0-6.5)
Median Survival (months) (95% CI) | 30.5* (26.8-ne) | 22.1* (17.6-28.9)

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

1 Estimated median survival

**Docetaxel in combination with capecitabine**

Data from one multicenter, randomised, controlled phase III clinical trial support the use of docetaxel in combination with capecitabine for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline. In this trial, 255 patients were randomised to treatment with docetaxel (75mg/m² as a 1 hour intravenous infusion every 3 weeks) and capecitabine (1250mg/m² twice daily for 2 weeks followed by 1-week rest period). 256 patients were randomised to treatment with docetaxel alone (100mg/m² as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel + capecitabine combination arm (p=0.0126). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6\% (docetaxel + capecitabine) vs. 29.7\% (docetaxel alone); p = 0.0058. Time to progressive disease was superior in the docetaxel + capecitabine combination arm (p < 0.0001). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone).

**Non-Small Cell Lung Cancer**

*Patients previously treated with chemotherapy with or without radiotherapy*

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

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

**Docetaxel in combination with platinum agents in chemotherapy-naïve patients**

In a Phase III trial, 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) 75mg/m² as a 1 hour infusion immediately followed by cisplatin (Cis) 75mg/ m² over 30-60 minutes every 3 weeks, docetaxel 75mg/ m² as a 1 hour infusion in combination with carboplatin (AUC 6mg/ml•min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25mg/ m² administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100mg/ m² administered on day 1 of cycles repeated every 4 weeks.

Survival data, median time to progression and response rates for two arms of the study are illustrated in the following table:
PAR Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion

UK/H/1917/001-002/DC

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

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

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

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

**Prostate Cancer**

The safety and efficacy of docetaxel in combination with prednisone or prednisolone in patients with hormone refractory metastatic prostate cancer were evaluated in a randomized multicenter Phase III trial. A total of 1006 patients with KPS ≥ 60 were randomized to the following treatment groups:
- Docetaxel 75mg/m² every 3 weeks for 10 cycles.
- Docetaxel 30mg/m² administered weekly for the first 5 weeks in a 6 week cycle for 5 cycles.
- Mitoxantrone 12mg/m² every 3 weeks for 10 cycles.

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

Patients who received docetaxel every three weeks demonstrated significantly longer overall survival compared to those treated with mitoxantrone. The increase in survival seen in the docetaxel weekly arm was not statistically significant compared to the mitoxantrone control arm. Efficacy endpoints for the docetaxel arms versus the control arm are summarized in the following table:
Given the fact that docetaxel every week presented a slightly better safety profile than docetaxel every 3 weeks, it is possible that certain patients may benefit from docetaxel every week.

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

**Gastric Adenocarcinoma**

A multicenter, open-label, randomized 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) (75mg/m² on day 1) in combination with cisplatin (C) (75mg/m² on day 1) and 5-fluorouracil (F) (750mg/m² per day for 5 days) or cisplatin (100mg/m² on day 1) and 5-fluorouracil (1000mg/m² per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p=0.0004) in favor of the TCF arm. Overall survival was also significantly longer (p=0.0201) in favor of the TCF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarized in the following table:
Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

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

*p-value

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

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

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

**Head and neck cancer**
- Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75mg/m² followed by cisplatin (P) 75mg/m² followed by 5-fluorouracil (F) 750mg/m² per day as a continuous infusion for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (TPF/RT). Patients on the comparator arm received cisplatin (P) 100mg/m² followed by 5-fluorouracil (F) 1000mg/m² per day for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (PF/RT). Locoregional therapy with radiation was delivered either with a conventional fraction (1.8 Gy - 2.0 Gy once a day, 5 days per week for a total dose of 66 Gy to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week). A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy.

Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 500mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p = 0.0042 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, p = 0.0128. Efficacy results are presented in the table below:
### Efficacy of docetaxel in the induction treatment of patients with inoperable locally advanced SCCHN (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Docetaxel+ Cis+5-FU</th>
<th>Cis+5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median progression free survival (months)</td>
<td>11.4 (10.1-14.0)</td>
<td>8.3 (7.4-9.1)</td>
</tr>
<tr>
<td>Adjusted Hazard ratio (95%CI)</td>
<td>0.70 (0.55-0.89)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Median survival (months) (95%CI)</td>
<td>18.6 (15.7-24.0)</td>
<td>14.5 (11.6-18.7)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>0.72 (0.56-0.93)</td>
<td>0.0128</td>
</tr>
<tr>
<td>Med. duration response to chemotherapy ± radiotherapy (months)</td>
<td>n=128 15.7 (13.4-24.6)</td>
<td>n=106 11.7 (10.2-17.4)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>0.72 (0.52-0.99)</td>
<td>0.0457</td>
</tr>
</tbody>
</table>

A Hazard ratio of less than 1 favors docetaxel+Cisplatin+5-FU

* Cox model (adjustment for Primary tumor site, T and N clinical stages and PSWHO)  
** Logrank test  
*** Chi-square test

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

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

Median time to first deterioration of WHO performance status was significantly longer in the TPF arm compared to PF. Pain intensity score improved during treatment in both groups indicating adequate pain management.

- **Induction chemotherapy followed by chemoradiotherapy (TAX324)**
  The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a randomized, multicenter open-label, phase III, trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two arms. The study population comprised patients with technically unresectable disease, patients with low probability of surgical cure and patients aiming at organ preservation. The efficacy and safety evaluation solely addressed survival endpoints and the success of organ preservation was not formally addressed. Patients on the docetaxel arm received docetaxel (T) 75mg/m² by intravenous infusion on day 1 followed by cisplatin (P) 100mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of 5-fluorouracil (F) 1000mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received...
cisplatin (P) 100mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of 5-fluourouracil (F) 1000mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).

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

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Docetaxel + Cis + 5-FU</th>
<th>Cis + 5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (months) (95% CI)</td>
<td>70.6 (49.0-NA)</td>
<td>30.1 (20.9-51.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI) *p-value</td>
<td>0.70 (0.54-0.90)</td>
<td>0.0058</td>
</tr>
<tr>
<td>Median PFS (months) (95% CI)</td>
<td>35.5 (19.3-NA)</td>
<td>13.1 (10.6-20.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI) **p-value</td>
<td>0.71 (0.56-0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td>Best overall response (CR+PR) to chemotherapy (%) (95% CI) ***p-value</td>
<td>71.8 (65.8-77.2)</td>
<td>64.2 (57.9-70.2)</td>
</tr>
<tr>
<td>Best overall response (CR+PR) to study treatment [chemotherapy +/- chemoradiotherapy] (%) (95% CI) ***p-value</td>
<td>76.5 (70.8-81.5)</td>
<td>71.5 (65.5-77.1)</td>
</tr>
</tbody>
</table>

A Hazard ratio of less than 1 favors docetaxel + cisplation + fluorouracil
* un-adjusted log-rank test
** un-adjusted log-rank test, not adjusted for multiple comparisons
*** Chi square test, not adjusted for multiple comparisons
NA – not applicable

### Pharmacokinetic properties

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115mg/m² in Phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the \( \alpha \), \( \beta \) and \( \gamma \) phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100mg/m² dose given as a one hour infusion a mean peak plasma level of 3.7µg/ml was obtained with a corresponding AUC of 4.6h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m² and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.
A study of $^{14}$C-docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and faeces following cytochrome P450-mediated oxidative metabolism of the tert-butyl ester group, within seven days, the urinary and faecal excretion accounted for about 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in faeces is excreted during the first 48 hours as one major inactive metabolite and 3 minor inactive metabolites and very low amounts of unchanged medicinal product.

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

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

Phase I study evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of docetaxel (C$_{\text{max}}$ 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 tumors had no influence on the pharmacokinetics of each individual drug.

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

5.3 Preclinical safety data

The carcinogenic potential of docetaxel has not been studied.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Concentrate vial:
- Citric acid anhydrous
- Ethanol absolute
- Polysorbate 80

Solvent vial:
- Ethanol absolute
- Water for injections

6.2 Incompatibilities

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

Docetaxel vials as packaged for sale: 24 months when stored below 25°C

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

- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at about 25°C at normal lighting conditions, and 4 hours at 5°C ± 3°C protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

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

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

6.5 Nature and contents of container

Each pack of Docetaxel is presented in a polystyrene Thermoformed tray for 2 vials which contains:

- one single dose Docetaxel vial of concentrate
- one single dose solvent for Docetaxel vial of concentrate

Docetaxel 20mg/0.5 ml concentrate for solution for infusion vial:

8ml clear borosilicate glass Type I vial with a bromobutylic rubber stopper and a metallic flip-off cap made of aluminium sheet with a polypropylene disk.

This vial contains 0.5ml of a 40mg/ml solution of docetaxel in citric acid anhydrous, polysorbate 80 and ethanol absolute (fill volume: 25.2mg/0.63ml). Solvent vial: 8ml clear borosilicate glass Type I vial with a bromobutylic rubber stopper and a metallic flip-off cap made of aluminium sheet with a polypropylene disk.

Solvent vial contains 1.5ml of a 9.53% w/w solution of ethanol absolute in water for injections (fill volume: 2.0ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel 20mg/0.5 ml concentrate for solution for infusion vial ensures a premix concentration of 10mg/ml docetaxel.

6.6 Special precautions for disposal

Docetaxel is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel solutions. The use of gloves is recommended. If Docetaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Docetaxel concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Fill volume

Docetaxel 20mg/0.5 ml concentrate for solution for infusion vial

The fill volume of 25.2mg/0.63ml has been established during the development of Docetaxel to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for Docetaxel vial, there is a minimal extractable premix volume of 2ml containing 10mg/ml docetaxel which corresponds to the labelled amount of 20mg/0.5ml per vial.

Preparation for the intravenous administration

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

If the vials are stored under refrigeration, allow the required number of Docetaxel boxes to stand at room temperature for 5 minutes.

Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel vial by partially inverting the vial.
Inject the entire contents of the syringe into the corresponding Docetaxel vial. Remove the syringe and needle and mix manually by repeated inversions for at least 120 seconds. Do not shake.

Allow the premix vial to stand for 3 minutes at room temperature and then check that the solution is homogenous and clear (foaming is normal even after 3 minutes due to the presence of polysorbate 80 in the formulation).

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

**b) Preparation of the infusion solution**

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

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

Mix the infusion bag or bottle manually using a rocking motion. The Docetaxel infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.

As with all parenteral products, Docetaxel premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.
1 NAME OF THE MEDICINAL PRODUCT
Docetaxel Actavis 80 mg/2 ml concentrate and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each single dose vial contains docetaxel 80 mg/2 ml.
Each single dose vial contains 40mg/ml of docetaxel.
Each single dose vial contains 10mg/ml of docetaxel after reconstitution with the accompanying solvent.

Excipients:
Each single dose 80 mg/2 ml vial of concentrate contains 200 mg ethanol absolute.
Each single dose vial of solvent contains 9.53% (w/w) ethanol absolute.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate and solvent for solution for infusion.
The concentrate is a clear, oily, yellow solution.
The solvent is a clear colourless solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

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

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

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

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

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

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

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

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

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

Head and neck cancer
Docetaxel in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.
4.2 **Posology and method of administration**

The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy. After reconstitution of the concentrate vial with the appropriate solvent, the premix solution should be homogeneous and clear (foaming is normal even after 3 minutes due to the presence of polysorbate 80 in the formulation). (See section 6.6 for instructions on the dilution of the product before administration).

**Recommended dosage**

For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg 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 hematological toxicities.

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

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

**Breast cancer**

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of docetaxel is 75mg/m² administered 1-hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² every 3 weeks for 6 cycles (see also Dosage adjustments during treatment).

For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dosage of docetaxel is 100mg/m² in monotherapy. In first-line treatment, docetaxel 75mg/m² is given in combination therapy with doxorubicin (50mg/m²).

In combination with trastuzumab the recommended dose of docetaxel is 100mg/m² every three weeks, with trastuzumab administered weekly. In the pivotal trial the initial docetaxel infusion was started the day following the first dose of trastuzumab. The subsequent docetaxel doses were administered immediately after completion of the trastuzumab infusion, if the preceding dose of trastuzumab was well tolerated. For trastuzumab dosage and administration, see trastuzumab summary of product characteristics.

In combination with capecitabine, the recommended dose of docetaxel is 75mg/m² every three weeks, combined with capecitabine at 1250mg/m² 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 75mg/m² immediately followed by cisplatin 75mg/m² over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dosage is 75mg/m² as a single agent.

**Prostate cancer**

The recommended dose of docetaxel is 75mg/m². Prednisone or prednisolone 5mg orally twice daily is administered continuously (see section 5.1).

**Gastric adenocarcinoma**

The recommended dose of docetaxel is 75mg/m² as a 1 hour infusion, followed by cisplatin 75mg/m², as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m² per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion.

Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of hematological toxicities (See also 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 hematological toxicities. All patients on the docetaxel-containing arm of the TAX 323 and TAX 324 studies, received prophylactic antibiotics.

- Induction chemotherapy followed by radiotherapy (TAX 323)

  For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of docetaxel is 75mg/m² as a 1 hour infusion followed by cisplatin 75mg/m² over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750mg/m² 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 75mg/m² as a 1 hour intravenous infusion on day 1, followed by cisplatin 100mg/m² administered as a 30-minute to 3 hour infusion, followed by 5-fluorouracil 1000mg/m²/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.

**Dosage adjustments during treatment**

**General**

Docetaxel should be administered when the neutrophil count is \( \geq 1,500 \text{cells/mm}^3 \). In patients who experienced either febrile neutropenia, neutrophil \(< 500 \text{cells/mm}^3 \) 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 100mg/m² to 75mg/m² and/or from 75 to 60mg/m². If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued.

**Adjuvant therapy for breast cancer**

In the pivotal trial in patients who received adjuvant therapy for breast cancer and who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (eg, day 4 to 11) in all subsequent cycles. Patients who continued to experience this reaction should remain on G-CSF and have their docetaxel dose reduced to 60mg/m².

However, in clinical practice neutropenia could occur earlier. Thus the use of G-CSF should be considered function of the neutropenic risk of the patient and current recommendations. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m².

**In combination with cisplatin**

For patients who are dosed initially at docetaxel 75mg/m² in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is \(< 25000 \text{cells/mm}^2 \), or in patients who experience febrile neutropenia, or in patients with serious non-hematologic toxicities, the docetaxel dosage in subsequent cycles should be reduced to 65mg/m². 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 55mg/m².
- For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the docetaxel dose.
For trastuzumab dose modifications, see trastuzumab summary of product characteristics.

**In combination with cisplatin and 5-fluorouracil:**
If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60mg/m². If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45mg/m². In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60mg/m². Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm³ and platelets recover to a level > 100,000 cells/mm³. 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):

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dosage adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea grade 3</td>
<td>First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.</td>
</tr>
<tr>
<td>Diarrhoea grade 4</td>
<td>First episode: reduce docetaxel and 5-FU doses by 20%. Second episode: discontinue treatment.</td>
</tr>
<tr>
<td>Stomatitis/mucositis grade 3</td>
<td>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%.</td>
</tr>
<tr>
<td>Stomatitis/mucositis grade 4</td>
<td>First episode: stop 5-FU only, at all subsequent cycles. Second episode: reduce docetaxel dose by 20%.</td>
</tr>
</tbody>
</table>

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

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

**Special populations**

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

In combination with cisplatin and 5-fluorouracil for the treatment of patients with gastric adenocarcinoma, the pivotal clinical trial excluded patients with ALT and/or AST > 1.5 × ULN associated with alkaline phosphatase > 2.5 × ULN, and bilirubin > 1 × 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)

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**4.3 Contraindications**
Hypersensitivity to the active substance or to any of the excipients. Docetaxel must not be used in patients with baseline neutrophil count of < 1,500 cells/mm³.
Docetaxel must not be used in patients with severe liver impairment since there is no data available (see sections 4.2 and 4.4). Contraindications for other medicinal products also apply, when combined with docetaxel.

4.4 Special warnings and precautions for use

For breast and non-small cell lung cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg 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 8mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see section 4.2).

Haematology

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

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

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

Hypersensitivity reactions

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

Cutaneous reactions

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

Fluid retention

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

Patients with liver impairment

In patients treated with docetaxel at 100mg/m$^2$ as single agent who have serum transaminase levels (ALT and/or AST) greater than 1.5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of docetaxel in those patients with elevated liver function test (LFTs) is 75mg/m$^2$ and LFTs should be measured at baseline and before each cycle (see section 4.2).

For patients with serum bilirubin levels > ULN and/or ALT and AST > 3.5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

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

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

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

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

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

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

**Additional cautions for use in adjuvant treatment of breast cancer**

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

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

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

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

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

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

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

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

**Ethanol**

Docetaxel contains 100mg of ethanol absolute per ml concentrate. The solvent contains 9.53\% (w/w) ethanol absolute. This may be harmful in patients suffering from alcoholism. The ethanol content of this medicinal product should be taken into account when used children or in high-risk groups such as patients with liver disease, or epilepsy.

### 4.5 Interaction with other medicinal products and other forms of interaction

There have been no formal clinical studies to evaluate the interactions of docetaxel with other medicinal products.

*In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporin, terfenadine, ketoconazole, erythromycin and troleandomycin. 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.

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

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

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

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

The ethanol content of this medicinal product may alter the effects of other medicines.

### 4.6 Pregnancy and lactation

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

*Women of childbearing potential / contraception:*

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

An effective method of contraception should be used during treatment.

In non clinical studies, docetaxel has genotoxic effects and may alter male fertility (see section 5.3). Therefore, men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.
**Lactation:**
Docetaxel is a lipophilic substance but it is not known whether it is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued for the duration of docetaxel therapy.

### 4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. The ethanol content of this medicinal product may impair the ability to drive or use machines.

### 4.8 Undesirable effects
The adverse reactions considered to be possibly or probably related to the administration of docetaxel have been obtained in:
- 1312 and 121 patients who received 100mg/m² and 75mg/m² of docetaxel as a single agent respectively
- 258 patients who received docetaxel in combination with doxorubicin
- 406 patients who received docetaxel in combination with cisplatin
- 92 patients treated with docetaxel in combination with trastuzumab,
- 255 patients who received docetaxel in combination with capecitabine,
- 332 patients who received docetaxel in combination with prednisone or prednisolone (clinically important treatment related adverse events are presented).
- 744 patients who received docetaxel in combination with doxorubicin and cyclophosphamide (clinically important treatment related adverse events are presented).
- 300 gastric adenocarcinoma patients (221 patients in the phase III part of the study and 79 patients in the phase II part) who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment related adverse events are presented).
- 174 and 251 head and neck cancer patients who received docetaxel in combination with cisplatin and 5-fluorouracil (clinically important treatment related adverse events are presented).

These reactions were described using the NCI Common Toxicity Criteria (grade 3 = G3; grade3-4 = G3/4; grade 4 = G4) and the COSTART terms. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

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/mm³) was 7 days), anemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of docetaxel may be increased when docetaxel is given in combination with other chemotherapeutic agents.

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

For combination with capecitabine, the most frequent treatment-related undesirable effects (≥ 5%) reported in a phase III 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 paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

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

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

**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 generalized rash/erythema (see section 4.4).

**Docetaxel 100mg/m² single agent:**

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>G3/4 Blood bilirubin increased (&lt;5%); G3/4 Blood alkaline phosphatase increased (&lt;4%); G3/4 AST increased (&lt;5%); G3/4 ALT increased (&lt;2%)</td>
<td>Cardiac failure</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmia (G3/4: 0.7%); Thrombocytopenia (G4: 0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%); Febrile neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3: 4.1%); Peripheral motor neuropathy (G3/4: 4%); Dysgeusia (severe 0.07%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea (severe 2.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Stomatitis (G3/4: 5.3%); Diarrhoea (G3/4: 4%); Nausea (G3/4: 4%); Vomiting (G3/4: 3%)</td>
<td>Constipation (severe 0.2%); Abdominal pain (severe 1%); Gastrointestinal Haemorrhage (severe 0.3%)</td>
<td>Oesophagitis (severe: 0.4%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Skin reaction (G3/4: 5.9%); Nail disorders (severe 2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia (severe 1.4%)</td>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)</td>
<td>Infection associated with G4 neutropenia (G3/4: 4.6%)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension; Hypertension; Haemorrhage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**MedDRA System Organ classes**

### Very common adverse reactions ≥ 1/10

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Fluid retention (severe: 6.5%); Askenia (severe 11.2%); Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4: 5.3%)</td>
</tr>
</tbody>
</table>

### Common adverse reactions ≥ 1/100, < 1/10

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Infusion site reaction; Non-cardiac chest pain (severe 0.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
</tbody>
</table>

### Uncommon adverse reactions ≥ 1/1000, < 1/100

### 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 100mg/m² as single agent. The events were spontaneously reversible within 3 months.

### Skin and subcutaneous tissue disorders

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

### General disorders and administration site conditions

The median cumulative dose to treatment discontinuation was more than 1,000mg/m² 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: 818.9mg/m²) in patients with premedication compared with patients without premedication (median cumulative dose: 489.7mg/m²); however, it has been reported in some patients during the early courses of therapy.

**Docetaxel 75mg/m² single agent:***

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td>G3/4 Blood bilirubin Increased (&lt;2%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Arrhythmia (no severe);</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)</td>
<td>Febrile neutropenia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3/4: 0.8%)</td>
<td>Peripheral motor neuropathy (G3/4: 2.5%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhoea (G3/4: 1.7%)</td>
<td>Constipation</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Skin reaction (G3/4: 0.8%)</td>
<td>Nail disorders (severe 0.8%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infections (G3/4: 5%)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (severe 12.4%); Fluid retention (severe 0.8%); Pain</td>
<td>Hypersensitivity (no severe)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Docetaxel 75mg/m² in combination with doxorubicin:

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions $\geq 1/10$</th>
<th>Common adverse reactions $\geq 1/100, &lt; 1/10$</th>
<th>Uncommon adverse reactions $\geq 1/1,000, &lt; 1/100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td>G3/4 Blood bilirubin increased ($\leq 2.5%$); G3/4 Blood alkaline phosphatase increased ($\leq 2.5%$)</td>
<td>G3/4 AST increased ($&lt; 1%$); G3/4 ALT increased ($&lt; 1%$)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Cardiac failure; Arrhythmia (no severe)</td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3: 0.4%); Peripheral motor neuropathy (G3/4: 0.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhoea (G3/4: 6.2%); Vomiting (G3/4: 5%); Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Nail disorders (severe 0.4%); Skin reaction (no severe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4: 7.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (severe 8.1%); Fluid retention (severe 1.2%); Pain</td>
<td>Infusion site reaction</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hyposensitivity (G3/4: 1.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Docetaxel 75mg/m² in combination with cisplatin:

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions $\geq 1/10$</th>
<th>Common adverse reactions $\geq 1/100, &lt; 1/10$</th>
<th>Uncommon adverse reactions $\geq 1/1,000, &lt; 1/100$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td>G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased (1.3%)</td>
<td>G3/4 AST increased (0.5%); G3/4 Blood alkaline phosphatase increased (0.3%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Arrhythmia (G3/4: 0.7%)</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4:0.5%)</td>
<td>Febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3: 3.7%); Peripheral motor neuropathy (G3/4: 2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA System Organ classes</td>
<td>Very common adverse reactions ≥ 1/10</td>
<td>Common adverse reactions ≥ 1/100, &lt; 1/10</td>
<td>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%)</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Nail disorders (severe 0.7%); Skin reaction (G3/4: 0.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia (severe 0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4: 5.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension (G3/4: 0.7%)</td>
<td>Infusion site reaction; Pain</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (severe 9.9%); Fluid retention (severe 0.7%); Fever (G3/4: 1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4: 2.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Docetaxel 100mg/m² in combination with trastuzumab:**

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G3/4: 32%); Febrile neutropenia (includes neutropenia associated with fever and antibiotic use) or neutropenic sepsis</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paresthesia; Headache; Dyseusia; Hypoaesthesia</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased; Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Epistaxis; Pharyngolaryngeal pain; Nasopharyngitis; Dyspnoea; Cough; Rhinorrhoea</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea; Diarrhoea; Vomiting; Constipation; Stomatitis; Dyspepsia; Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Erythema; Rash; Nail disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia; Arthralgia; Pain in extremity; Bone pain; Back pain</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Lymphoedema</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia; Oedema peripheral; Pyrexia; Fatigue; Mucosal inflammation; Pain; Influenza like illness; Chest pain; Chills</td>
<td>Lethargy</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td></td>
</tr>
</tbody>
</table>
**Cardiac disorders**
Symptomatic cardiac failure was reported in 2.2% of the patients who received docetaxel plus trastuzumab compared to 0% of patients given docetaxel alone. In the docetaxel plus trastuzumab arm, 64% had received a prior anthracycline as adjuvant therapy compared with 55% in the docetaxel arm alone.

**Blood and the lymphatic system disorders**
Very common: Haematological toxicity was increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m² is known to result in neutropenia in 97% of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

**Docetaxel 75mg/m² in combination with capecitabine:**

<table>
<thead>
<tr>
<th>Organs</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased;</td>
<td>G3/4 Blood bilirubin increased (9%)</td>
</tr>
<tr>
<td>Blood and the lymphatic</td>
<td>Neutropenia (G3/4: 63%);</td>
<td>Thrombocytopenia (G3/4: 3%)</td>
</tr>
<tr>
<td>system disorders</td>
<td>Anaemia (G3/4: 10%)</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia (G3/4: &lt;1%);</td>
<td>Dizziness;</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia (G3/4: &lt;1%)</td>
<td>Headache (G3/4: &lt;1%);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathy peripheral</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic</td>
<td>Pharyngolaryngeal pain</td>
<td>Dyspnoea (G3/4: 1%);</td>
</tr>
<tr>
<td>and mediastinal disorders</td>
<td>(G3/4: 2%)</td>
<td>Cough (G3/4: &lt;1%);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epistaxis (G3/4: &lt;1%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Stomatitis (G3/4: 18%);</td>
<td>Abdominal pain upper;</td>
</tr>
<tr>
<td>disorders</td>
<td>Diarrhoea (G3/4: 14%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea (G3/4: 6%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting (G3/4: 4%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation (G3/4: 1%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain (G3/4: 2%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>Hand-foot syndrome (G3/4: 24%);</td>
<td>Dermatitis;</td>
</tr>
<tr>
<td>tissue disorders</td>
<td>Alopecia (G3/4: 6%);</td>
<td>Rash erythematous (G3/4: &lt;1%);</td>
</tr>
<tr>
<td></td>
<td>Nail disorders (G3/4: 2%)</td>
<td>Nail discolouration;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Onycholysis (G3/4: 1%)</td>
</tr>
<tr>
<td>Musculoskeletal and</td>
<td>Myalgia (G3/4: 2%);</td>
<td>Pain in extremity (G3/4: &lt;1%);</td>
</tr>
<tr>
<td>connective tissue</td>
<td>Arthralgia (G3/4: 1%)</td>
<td>Back pain (G3/4: 1%);</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Anorexia (G3/4: 1%);</td>
<td>Dehydration (G3/4: 2%);</td>
</tr>
<tr>
<td>disorders</td>
<td>Decreased appetite</td>
<td></td>
</tr>
<tr>
<td>Infections and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>infestations</td>
<td>Oral candidiasis (G3/4: &lt;1%)</td>
<td></td>
</tr>
<tr>
<td>General disorders and</td>
<td>Asthenia (G3/4: 3%);</td>
<td>Lethargy;</td>
</tr>
<tr>
<td>administration site</td>
<td>Pyrexia (G3/4: 1%);</td>
<td>Pain</td>
</tr>
<tr>
<td>conditions</td>
<td>Fatigue/ weakness (G3/4: 5%);</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oedema peripheral (G3/4: 1%);</td>
<td></td>
</tr>
</tbody>
</table>

**Docetaxel 75mg/m² in combination with prednisone or prednisolone:**

<table>
<thead>
<tr>
<th>Organs</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac left ventricular function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>decrease (G3/4: 0.3%)</td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic</td>
<td>Neutropenia (G3/4: 32%);</td>
<td>Thrombocytopenia;</td>
</tr>
<tr>
<td>system disorders</td>
<td>Anaemia (G3/4: 4.9%)</td>
<td>(G3/4: 0.6%);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile neutropenia</td>
</tr>
</tbody>
</table>
| Nervous system disorders| Peripheral sensory neuropathy        | Peripheral motor neuropathy (G3/4: 0%)
|                         | (G3/4: 1.2%);                        |                                       |
|                         | Dysgeusia (G3/4: 0%)                 |                                       |
### MedDRA System Organ classes

<table>
<thead>
<tr>
<th>Very common adverse reactions</th>
<th>Common adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye disorders</strong></td>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
</tr>
<tr>
<td>Lacrimation increased (G3/4: 0.6%)</td>
<td>Epistaxis (G3/4: 0%); Dyspnœa (G3/4: 0.6%); Cough (G3/4: 0%)</td>
</tr>
</tbody>
</table>

| **Gastrointestinal disorders** | **Skin and subcutaneous tissue disorders** |
| Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%) | Alopecia; Nail disorders (no severe) |

| **Musculoskeletal and connective tissue disorders.** | **Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)** |
| **Infections and infestations** | **Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)** |

| **Immune system disorders** | **Hypersensitivity (G3/4: 0.6%)** |
| **Docetaxel 75mg/m² in combination with doxorubicin and cyclophosphamide:** |

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions</th>
<th>Common adverse reactions</th>
<th>Uncommon adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td>Weight increased or decreased (G3/4: 0.3%)</td>
<td>Arrhythmia (G3/4: 0.1%); Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Anaemia (G3/4: 4.3%); Neutropenia (G3/4: 65.5%); Thrombocytopenia (G3/4: 2.0%); Febrile neutropenia</td>
<td>Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebella (G3/4: 0.1%)</td>
<td>Syncope (G3/4: 0%)</td>
</tr>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td>Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Cough (G3/4: 0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Nausea (G3/4: 5.1%); Stomatitis (G3/4: 7.1%); Vomiting (G3/4: 4.3%); Diarrhoea (G3/4: 3.2%); Constipation (G3/4: 0.4%)</td>
<td>Abdominal pain (G3/4:0.5%)</td>
<td>Colitis/enteritis/ large intestine perforation</td>
</tr>
</tbody>
</table>
### MedDRA System Organ classes

<table>
<thead>
<tr>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia; Skin toxicity (G3/4: 0.7%); Nail disorders (G3/4: 0.4%)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders.</td>
<td>Myalgia (G3/4: 0.8%); Arthralgia (G3/4: 0.4%)</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4: 2.2%)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4: 3.2%); Neutropenic infection. There were no septic deaths</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasodilatation (G3/4: 0.9%)</td>
<td>Hypotension (G3/4: 0%); Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia (G3/4: 11%); Fever (G3/4: 1.2%); Oedema peripheral (G3/4: 0.4%)</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4: 1.1%)</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Amenorrhoea</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiac disorders**

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

**Nervous system disorders**

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

**Skin and subcutaneous tissue disorders**

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

**General disorders and administration site conditions**

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

**Reproductive system and breast disorders**

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

**Cardiac disorders**

Cardiac disorders

Cardiovascular events were uncommon and included atrial fibrillation, supraventricular tachycardia, angina, and atrioventricular blocks. One patient in each treatment arm died due to cardiac failure.

**Nervous system disorders**

Nervous system disorders

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

**Skin and subcutaneous tissue disorders**

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

**General disorders and administration site conditions**

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

**Reproductive system and breast disorders**

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

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

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Anaemia (G3/4: 20.9%); Neutropenia (G3/4: 83.2%); Thrombocytopenia (G3/4: 8.8%); Febrile neutropenia</td>
<td>Arrhythmia (G3/4: 1.0%).</td>
</tr>
<tr>
<td>MedDRA System Organ classes</td>
<td>Very common adverse reactions ≥ 1/10</td>
<td>Common adverse reactions ≥ 1/100, &lt; 1/10</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Peripheral sensory neuropathy (G3/4: 8.7%)</td>
<td>Dizziness (G3/4: 2.3%); Peripheral motor neuropathy (G3/4: 1.3%).</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased (G3/4: 0%)</td>
<td>Hearing impaired (G3/4: 0%).</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Diarrhoea (G3/4: 19.7%); Nausea (G3/4: 16%); Stomatitis (G3/4: 23.7%); Vomiting (G3/4: 14.3%).</td>
<td>Constipation (G3/4: 1.0 %); Gastrointestinal pain (G3/4: 1.6%); Oesophagitis/dysphagia/odynophagia (G3/4: 0.7%).</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia (G3/4: 4.0%)</td>
<td>Rash pruritus (G3/4: 0.7%); Nail disorders (G3/4: 0.7%); Skin exfoliation (G3/4: 0%).</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4: 11.7%)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Neutropenic infection; Infection (G3/4: 11.7%).</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Lethargy (G3/4: 19.0%); Fever (G3/4: 2.3%); Fluid retention (severe/life-threatening: 1%).</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity (G3/4:1.7).</td>
<td></td>
</tr>
</tbody>
</table>

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

**Docetaxel 75mg/m² in combination with cisplatin and 5-fluorouracil for Head and Neck cancer:**
- Induction chemotherapy followed by radiotherapy (TAX 323)

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight increased</td>
<td>Myocardial ischemia (G3/4:1.7%)</td>
<td>Arrhythmia (G3/4:0.6%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutropenia (G3/4:76.3%); Anemia (G3/4:9.2); Thrombocytopenia (G3/4:5.2%)</td>
<td>Febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia/Parosmia Peripheral sensory neuropathy (G3/4:0.6%)</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Lacrimation increased Conjunctivitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hearing impaired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4:0.6%); Stomatitis (G3/4:4.0%); Diarrhoea (G3/4:2.9%); Vomiting (G3/4:0.6%)</td>
<td>Constipation Esophagitis/ dysphagia/odynophagia (G3/4:0.6%); Abdominal pain Dyspepsia Gastrointestinal haemorrhage (G3/4:0.6%)</td>
<td></td>
</tr>
<tr>
<td>MedDRA System Organ classes</td>
<td>Very common adverse reactions ≥ 1/10</td>
<td>Common adverse reactions ≥ 1/100, &lt; 1/10</td>
<td>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia (G3/4:10.9%). Rash pruritic Dry skin Skin exfoliative (G3/4:0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia (G3/4:0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4:0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4:6.3%) Neutropenic infection</td>
<td>Cancer pain (G3/4:0.6%)</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Lethargy (G3/4:3.4%) Pyrexia (G3/4:0.6%) Fluid retention Oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Venous disorder (G3/4:0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity (no severe)</td>
<td></td>
</tr>
</tbody>
</table>

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

<table>
<thead>
<tr>
<th>MedDRA System Organ classes</th>
<th>Very common adverse reactions ≥ 1/10</th>
<th>Common adverse reactions ≥ 1/100, &lt; 1/10</th>
<th>Uncommon adverse reactions ≥ 1/1,000, &lt; 1/100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>Arrhythmia (G3/4:2.0%)</td>
<td>Ischemia myocardial</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Neutopenia (G3/4:83.5%) Anemia (G3/4:12.4%) Thrombocytopenia (G3/4:4.0%) Febrile neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysegeusia/Parosmia (G3/4:0.4%); Peripheral sensory neuropathy (G3/4:1.2%)</td>
<td>Dizziness (G3/4:2.0%); Peripheral motor neuropathy (G3/4:0.4%)</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>Lacrimation increased</td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hearing impaired (G3/4:1.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea (G3/4: 13.9%); Stomatitis (G3/4:20.7%); Vomiting (G3/4:8.4%); Diarrhoea (G3/4: 6.8%); Esophagitis/dysphagia/odynophagia (G3/4:12.0%); Constipation (G3/4:0.4%)</td>
<td>Dyspepsia (G3/4:0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4:0.4%)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia (G3/4:4.0%); Rash pruritic</td>
<td>Dry skin; Desquamation</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Myalgia (G3/4:0.4%)</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia (G3/4:12.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Infection (G3/4:3.6%)</td>
<td>Neutropenic infection</td>
<td></td>
</tr>
</tbody>
</table>
MedDRA System Organ classes | Very common adverse reactions \( \geq 1/10 \) | Common adverse reactions \( \geq 1/100, < 1/10 \) | Uncommon adverse reactions \( \geq 1/1,000, < 1/100 \)
--- | --- | --- | ---
Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  | Cancer pain (G3/4: 1.2\%) |  
Vascular disorders |  | Venous disorder |  
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

Post-Marketing Experience:

**Cardiac disorders**
Rare cases of myocardial infarction have been reported.

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

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

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

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

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

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

**Neoplasms benign, malignant and unspecified (incl 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. Fluid retention has not been accompanied by acute episodes of oliguria or hypotension. Dehydration and pulmonary oedema have rarely been reported.

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

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Antineoplastic agents, ATC Code: L01CD 02

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

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

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

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

An interim analysis was performed with a median follow up of 55 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was demonstrated. Incidence of relapses at 5 years was reduced in patients receiving TAC compared to those who received FAC (25% versus 32%, respectively) i.e. an absolute risk reduction by 7% (\( p=0.001 \)). Overall survival at 5 years was also significantly increased with TAC compared to FAC (87% versus 81%, respectively) i.e. an
absolute reduction of the risk of death by 6% (p=0.008). TAC-treated patient subsets according to prospectively defined major prognostic factors were analyzed:

<table>
<thead>
<tr>
<th>Patient subset</th>
<th>Number of patients</th>
<th>Hazard ratio*</th>
<th>95% CI</th>
<th>P=</th>
<th>Hazard ratio*</th>
<th>95% CI</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of positive nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>745</td>
<td>0.72</td>
<td>0.59-0.83</td>
<td>0.001</td>
<td>0.70</td>
<td>0.53-0.91</td>
<td>0.008</td>
</tr>
<tr>
<td>1-3</td>
<td>467</td>
<td>0.61</td>
<td>0.46-0.82</td>
<td>0.009</td>
<td>0.45</td>
<td>0.29-0.70</td>
<td>0.0002</td>
</tr>
<tr>
<td>4+</td>
<td>278</td>
<td>0.83</td>
<td>0.63-1.08</td>
<td>0.17</td>
<td>0.94</td>
<td>0.66-1.33</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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

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

**Docetaxel as single agent**

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

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

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

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

An open-label, multicenter, randomized phase III study was conducted to compare docetaxel monotherapy and paclitaxel in the treatment of advanced breast cancer in patients whose previous therapy should have included an anthracycline. A total of 449 patients were randomized to receive either docetaxel monotherapy 100mg/m² as a 1 hour infusion or paclitaxel 175mg/m² as a 3 hour infusion. Both regimens were administered every 3 weeks.

Without affecting the primary endpoint, overall response rate (32% vs 25%, p=0.10), docetaxel prolonged median time to progression (24.6 weeks vs 15.6 weeks; p < 0.01) and median survival (15.3 months vs 12.7 months; p=0.03).

More grade 3/4 adverse events were observed for docetaxel monotherapy (55.4%) compared to paclitaxel (23%).

**Docetaxel in combination with doxorubicin**

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

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

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

**Docetaxel in combination with trastuzumab**

Docetaxel in combination with trastuzumab was studied for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2, and who previously had not received chemotherapy for metastatic disease. One hundred eighty six patients were randomized to receive docetaxel (100mg/m²) with or without trastuzumab; 60% of patients received prior anthracycline-based adjuvant chemotherapy. Docetaxel plus trastuzumab was efficacious in patients whether or not they had received prior adjuvant anthracyclines. The main test method used to determine HER2 positivity in this pivotal trial was immunohistochemistry (IHC). A minority of patients were tested using fluorescence in-situ hybridization (FISH). In this trial, 87% of patients had disease that was IHC 3+, and 95% of patients entered had disease that was IHC 3+ and/or FISH positive. Efficacy results are summarized in the following table:

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

TTP=time to progression; “ne” indicates that it could not be estimated or it was not yet reached.

\(^1\)Full analysis set (intent-to-treat)

\(^2\)Estimated median survival

**Docetaxel in combination with capecitabine**

Data from one multicenter, randomised, controlled phase III clinical trial support the use of docetaxel in combination with capecitabine for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline. In this trial, 255 patients were randomised to treatment with docetaxel (75mg/m² as a 1 hour intravenous infusion every 3 weeks) and capecitabine (1250mg/m² twice daily for 2 weeks followed by 1-week rest period). 256 patients were randomised to treatment with docetaxel alone (100mg/m² as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel +capecitabine combination arm ($p=0.0126$). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (docetaxel + capecitabine) vs. 29.7% (docetaxel alone); $p = 0.0058$. Time to progressive disease
was superior in the docetaxel + capecitabine combination arm (p < 0.0001). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone).

**Non-Small Cell Lung Cancer**

*Patients previously treated with chemotherapy with or without radiotherapy*

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

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

**Docetaxel in combination with platinum agents in chemotherapy-naïve patients**

In a Phase III trial, 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) 75mg/m² as a 1 hour infusion immediately followed by cisplatin (Cis) 75mg/ m² over 30-60 minutes every 3 weeks, docetaxel 75mg/ m² as a 1 hour infusion in combination with carboplatin (AUC 6mg/ml•min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25mg/ m² administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100mg/ m² administered on day 1 of cycles repeated every 4 weeks.

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

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

*: 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 randomized multicenter Phase III trial. A total of 1006 patients with KPS ≥ 60 were randomized to the following treatment groups:

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

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

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Docetaxel every 3 weeks</th>
<th>Docetaxel every week</th>
<th>Mitoxantrone every 3 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>335</td>
<td>334</td>
<td>337</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>18.9 (17.0-21.2)</td>
<td>17.4 (15.7-19.0)</td>
<td>16.5 (14.4-18.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.761</td>
<td>0.912</td>
<td>--</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.0094</td>
<td>0.761</td>
<td>--</td>
</tr>
<tr>
<td>p-value*†</td>
<td></td>
<td>0.0094</td>
<td>--</td>
</tr>
</tbody>
</table>

| Number of patients             | 291                     | 282                  | 300                       |
| PSA** response rate (%)        | 45.4 (39.5-51.3)        | 47.9 (41.9-53.9)     | 31.7 (26.4-37.3)          |
| 95% CI                         | 0.0005                  | <0.0001              | --                        |
| p-value*†                      |                         | 0.0005               | --                        |

| Number of patients             | 153                     | 154                  | 157                       |
| Pain response rate (%)         | 34.6 (27.1-42.7)        | 31.2 (24.0-39.1)     | 21.7 (15.5-28.9)          |
| 95% CI                         | 0.0107                  | 0.0798               | --                        |
| p-value*†                      |                         | 0.0107               | --                        |

| Number of patients             | 141                     | 134                  | 137                       |
| Tumor response rate (%)        | 12.1 (7.2-18.6)         | 8.2 (4.2-14.2)       | 6.6 (3.0-12.1)            |
| 95% CI                         | 0.1112                  | 0.5853               | --                        |
| p-value*†                      |                         | 0.1112               | --                        |

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

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

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

**Gastric Adenocarcinoma**

A multicenter, open-label, randomized 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) (75mg/m² on day 1) in combination with cisplatin (C) (75mg/m² on day 1) and 5-fluorouracil (F) (750mg/m² per day for 5 days) or cisplatin (100mg/m² on day 1) and 5-fluorouracil (1000mg/m² per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p=0.0004) in favor of the TCF arm. Overall survival was also significantly longer (p=0.0201) in
favor of the TCF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarized in the following table:

Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP (months)</td>
<td>5.6</td>
<td>3.7</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(4.86-5.91)</td>
<td>(3.45-4.47)</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.473</td>
<td>1.825</td>
</tr>
<tr>
<td>*p-value</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>9.2</td>
<td>8.6</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(8.38-10.58)</td>
<td>(7.16-9.46)</td>
</tr>
<tr>
<td>2-year estimate (%)</td>
<td>18.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Hazard ratio (95%CI)</td>
<td>1.293</td>
<td>1.606</td>
</tr>
<tr>
<td>*p-value</td>
<td>0.0201</td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate (CR+PR) (%)</td>
<td>36.7</td>
<td>25.4</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0106</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease as Best Overall</td>
<td>16.7</td>
<td>25.9</td>
</tr>
<tr>
<td>Response (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Unstratified logrank test

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

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

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

**Head and neck cancer**

- Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicenter, open-label, randomized trial (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75mg/m² followed by cisplatin (P) 75mg/m² followed by 5-fluorouracil (F) 750mg/m² per day as a continuous infusion for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (TPF/RT). Patients on the comparator arm received cisplatin (P) 100mg/m² followed by 5-fluorouracil (F) 1000mg/m² per day for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (PF/RT). Locoregional therapy with radiation was delivered either with a conventional fraction (1.8 Gy - 2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week). A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy.

Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 500mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent. The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p =
0.0042 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, \( p = 0.0128 \). Efficacy results are presented in the table below:

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

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

A Hazard ratio of less than 1 favors docetaxel+Cisplatin+5-FU
*Cox model (adjustment for Primary tumor site, T and N clinical stages and PSWHO)
**Logrank test
*** Chi-square test

**Quality of life parameters**

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

**Clinical benefit parameters**

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

Median time to first deterioration of WHO performance status was significantly longer in the TPF arm compared to PF. Pain intensity score improved during treatment in both groups indicating adequate pain management.

- **Induction chemotherapy followed by chemoradiotherapy (TAX324)**

The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a randomized, multicenter open-label, phase III, trial (TAX324). In this study, 501 patients, with locally advanced SCCHN, and a WHO performance status of 0 or 1, were randomized to one of two arms. The study population comprised patients with technically unresectable disease, patients with low probability of surgical cure and patients aiming at organ preservation. The efficacy and safety evaluation solely addressed survival endpoints and the success of organ preservation was not formally addressed. Patients on the docetaxel arm received docetaxel (T) 75mg/m² by intravenous infusion on day 1 followed by cisplatin (P).
100mg/m² administered as a 30-minute to three-hour intravenous infusion, followed by the continuous intravenous infusion of 5-fluorouracil (F) 1000mg/m²/day from day 1 to day 4. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100mg/m² as a 30-minute to three-hour intravenous infusion on day 1 followed by the continuous intravenous infusion of 5-fluorouracil (F) 1000mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).

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

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

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Docetaxel + Cis + 5-FU n=225</th>
<th>Cis + 5-FU n=246</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (months) (95% CI)</td>
<td>70.6 (49.0-NA)</td>
<td>30.1 (20.9-51.5)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.54-0.90)</td>
<td>0.0058</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (months) (95% CI)</td>
<td>35.5 (19.3-NA)</td>
<td>13.1 (10.6-20.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.71 (0.56-0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best overall response (CR+PR) to chemotherapy (%) (95% CI)</td>
<td>71.8 (65.8-77.2)</td>
<td>64.2 (57.9-70.2)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td>Best overall response (CR+PR) to study treatment [chemotherapy +/- chemoradiotherapy] (%) (95% CI)</td>
<td>76.5 (70.8-81.5)</td>
<td>71.5 (65.5-77.1)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>0.209</td>
<td></td>
</tr>
</tbody>
</table>

A Hazard ratio of less than 1 favors docetaxel + cisplation + fluorouracil
*un-adjusted log-rank test
**un-adjusted log-rank test, not adjusted for multiple comparisons
***Chi square test, not adjusted for multiple comparisons
NA – not applicable

**5.2 Pharmacokinetic properties**

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115mg/m² in Phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the \( \alpha \), \( \beta \) and \( \gamma \) phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100mg/m² dose given as a one hour infusion...
a mean peak plasma level of 3.7µg/ml was obtained with a corresponding AUC of 4.6h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m² and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

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

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

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

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

Clearance of docetaxel in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after docetaxel infusion is similar to that observed with cisplatin alone. The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

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

5.3 Preclinical safety data
The carcinogenic potential of docetaxel has not been studied.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Concentrate vial:
Citric acid anhydrous
Ethanol absolute
Polysorbate 80

Solvent vial:
Ethanol absolute
Water for injections
6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life
Docetaxel vials as packaged for sale: 24 months when stored below 25°C

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

- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at about 25°C at normal lighting conditions, and 4 hours at 5°C ± 3°C protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

6.5 Nature and contents of container
Each pack of Docetaxel is presented in a polystyrene Thermoformed tray for 2 vials which contains:
- one single dose Docetaxel vial of concentrate
- one single dose solvent for Docetaxel vial of concentrate

Docetaxel 80 mg/2 ml concentrate for solution for infusion vial:
15 ml clear glass Type I vial with a bromobutilic rubber stopper and a metallic flip-off cap made of aluminium sheet with a polypropylene disk.

This vial contains 2 ml of a 40 mg/ml solution of docetaxel in citric acid anhydrous, polysorbate 80 and ethanol absolute (fill volume: 92.0 mg/2.3 ml). Solvent vial: 15 ml clear borosilicate glass Type I vial with a bromobutilic rubber stopper and a metallic flip-off cap made of aluminium sheet with a polypropylene disk.

Solvent vial contains 6 ml of a 9.53% w/w solution of ethanol absolute in water for injections (fill volume: 7.04 ml). The addition of the entire contents of the solvent vial to the contents of the /…/80 mg/2 ml concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml docetaxel.

6.6 Special precautions for disposal
Docetaxel is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel solutions. The use of gloves is recommended. If Docetaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Docetaxel concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Fill volume
Docetaxel 80 mg/2 ml concentrate for solution for infusion vial:
The fill volume of (fill volume: 92.0 mg/2.3 ml) has been established during the development of /…/ to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for /…/ vial, there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labelled amount of 80 mg/2 ml per vial.
Preparation for the intravenous administration

a) Preparation of the Docetaxel premix solution (10mg docetaxel/ml)
If the vials are stored under refrigeration, allow the required number of Docetaxel boxes to stand at room temperature for 5 minutes.

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

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

Remove the syringe and needle and mix manually by repeated inversions for at least 120 seconds. Do not shake.

Allow the premix vial to stand for 3 minutes at room temperature and then check that the solution is homogenous and clear (foaming is normal even after 3 minutes due to the presence of polysorbate 80 in the formulation).

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

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

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

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

Mix the infusion bag or bottle manually using a rocking motion. The Docetaxel infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.

As with all parenteral products, Docetaxel premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3
Product Information Leaflet

Docetaxel 20mg/0.5ml and 80mg/2ml Concentrate and Solvent for Solution for Infusion

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your hospital pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your hospital pharmacist.
- The full name of this medicine is Docetaxel 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion but within the leaflet it will be referred to as Docetaxel.

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

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

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

Pregnancy
Ask your doctor for advice before being given any medicine.

Docetaxel must not be administered if you are pregnant unless clearly indicated by your doctor.

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

If you are a man being treated with Docetaxel you are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because docetaxel may alter male fertility.

Breast-feeding
You must not breast-feed while you are treated with Docetaxel.

In this leaflet:
1. What Docetaxel is and what it is used for
2. Before you use
3. How to use
4. Possible side effects
5. How to store
6. Further information

1. What Docetaxel is and what it is used for
The name of this medicine is Docetaxel. Docetaxel is a substance derived from the needles of yew trees. Docetaxel belongs to the group of anti-cancer medicines called taxoids.

Docetaxel has been prescribed by your doctor for the treatment of breast cancer, special forms of lung cancer (non-small cell lung cancer), prostate cancer, gastric cancer or head and neck cancer:
- For the treatment of advanced breast
cancer, Docetaxel could be administered either alone or in combination with doxorubicin, or trastuzumab, or capecitabine.

- For the treatment of early breast cancer with lymph node involvement, Docetaxel could be administered in combination with doxorubicin and cyclophosphamide.
- For the treatment of lung cancer, Docetaxel could be administered either alone or in combination with cisplatin.
- For the treatment of prostate cancer, Docetaxel is administered in combination with prednisone or prednisolone.
- For the treatment of metastatic gastric cancer, Docetaxel is administered in combination with cisplatin and 5-fluorouracil.
- For the treatment of head and neck cancer, Docetaxel is administered in combination with cisplatin and 5-fluorouracil.

2. Before you use

Do not use Docetaxel if

- you are allergic (hypersensitive) to Docetaxel or any other ingredients of Docetaxel (See section 6).
- the number of white blood cells is too low.
- you have a severe liver disease.

Take special care with Docetaxel

Before each treatment with Docetaxel, you will have blood tests to check that you have enough blood cells and sufficient liver function to receive Docetaxel. In case of white blood cells disturbances, you may experience associated fever or infections. You will be asked to take premedication consisting of an oral corticosteroid such as dexamethasone, one day prior to Docetaxel administration and to continue for one or two days after it in order to minimise certain undesirable effects which may occur after the infusion of Docetaxel in particular allergic reactions and fluid retention (swelling of the hands, feet, legs or weight gain).

Driving and using machines

The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

There is no reason why you cannot drive between courses of Docetaxel except if you feel dizzy or are unsure of yourself.

Important information about one of the ingredients of Docetaxel

This medicinal product contains ethanol. Harmful for those suffering from alcoholism. To be taken into account in children and high risk groups such as patients with liver disease or epilepsy.

3. How to use

Docetaxel will be administered to you by a healthcare professional.

Usual dosage

The dose will depend on your weight and your general condition. Your doctor will calculate your body surface area in square meters (m²) and will determine the dose you should receive.

Method and route of administration

Docetaxel will be given by infusion into one of your veins. Docetaxel comes in 2 parts, a single vial of concentrate and a single vial of solvent. The infusion is made by diluting the contents of the concentrate vial with the contents of the solvent vial and then the resultant 'premix' solution is diluted with an appropriate infusion solution before being administered. The infusion will last approximately one hour during which you will be in the hospital.

Frequency of administration

You should usually receive your infusion once every 3 weeks.
Your doctor may change the dose and frequency of dosing depending on your blood tests, your general condition and your response to Docetaxel. In particular, please inform your doctor in case of diarrhoea, sores in the mouth, feeling of numbness or pins and needles, fever and give her/him results of your blood tests. Such information will allow her/him to decide whether a dose reduction is needed. If you have any further questions on the use of this product, ask your doctor, or hospital pharmacist.

4. Possible side effects

Like all other anticancer medicines, Docetaxel can cause side effects, although not everybody gets them.

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

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

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

During the infusion at the hospital the following allergic reactions (experienced in more than 1 person in 10) may occur:
• flushing, skin reactions, itching,
• chest tightness; difficulty in breathing,
• fever or chills,
• back pain
• low blood pressure
More severe reactions may occur.

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

Between infusions of Docetaxel the following may occur, and the frequency may vary with the combinations of drugs that are received:
• heart failure
• oesophagitis
• dry mouth
• difficulty or painful swallowing
• haemorrhage
• raised liver enzymes (hence the need for regular blood tests)

Uncommon: (experienced in more than 1 in 1,000 but less than 1 in 100)
• fainting
• at the injection site, skin reactions, phlebitis (inflammation of the vein) or swelling
• inflammation of the colon, small intestine; intestinal perforation
• blood clots

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or hospital pharmacist.

5. How to store

Keep out of the reach and sight of children. Docetaxel should not be used after the expiry date shown on the carton and vials. Do not store above 25°C. Store in the original package in order to protect from light.

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

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

6. Further information

What Docetaxel contains
• The active substance is docetaxel. Each ml of docetaxel solution contains 40mg of docetaxel anhydrous. One vial contains 20mg/0.5ml or 80mg/2ml of docetaxel.
• The other ingredients are citric acid anhydrous, ethanol absolute and polysorbate 80.
The solvent vial contains 9.53% w/w ethanol absolute in water for injections.
**Very Common:** (experienced in more than 1 in 10 patients)
- infections, decrease in the number of red (anaemia), or white blood cells (which are important in fighting infection) and platelets,
- fever; if this happens you must tell your doctor immediately
- allergic reactions as described above
- loss of appetite (anorexia)
- insomnia
- feeling of numbness or pins and needles or pain in the joints of muscles
- headache
- alteration in sense of taste
- inflammation of the eye or increased tearing of the eyes
- swelling caused by faulty lymphatic drainage
- shortness of breath
- nasal drainage; inflammation of the throat and nose; cough
- bleeding from the nose
- sores in the mouth
- stomach upsets including nausea, vomiting and diarrhoea, constipation
- abdominal pain
- indigestion
- short term hair loss (in most cases normal hair growth should return)
- redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel (this may also occur on the arms, face, or body)
- change in the color of your nails, which may detach
- muscle aches and pains; back pain or bone pain
- change or absence of menstrual period
- swelling of the hands, feet, legs
- tiredness; or flu-like symptoms
- weight gain or loss

**What Docetaxel looks like and contents of the pack**
Docetaxel concentrate for solution for infusion is a clear, oily, yellow solution. The solvent is a clear, colourless solution.

Each carton contains
Docetaxel 20mg/0.5ml
- one single dose vial of concentrate and
- one single dose vial of solvent

Docetaxel 80mg/2ml
- one single dose vial of concentrate and
- one single dose vial of solvent

**Marketing Authorisation Holder**
Actavis Group PTC ehf
Reykjavikurvsgur 76-78
Hafnarfjordur
IS-220
Iceland

**Manufacturer**
S.C. Sindan-Pharma S.R.L
11 Ion Mihalache Blvd
011171 Bucharest
Romania

**This leaflet was revised – April 2010**

If you would like a leaflet with larger text, please contact 01271 311257.
The following information is intended for medical or healthcare professionals only:

**PREPARATION GUIDE FOR USE WITH DOCETAXEL CONCENTRATE FOR SOLUTION FOR INFUSION AND SOLVENT**

*It is important to read the entire contents of this procedure prior to the preparation of either the Docetaxel premix solution or the Docetaxel infusion solution.*

### 1. FORMULATION

**Docetaxel 20mg/0.5ml**
Each blister pack contains:
- one single dose Docetaxel vial of concentrate 20mg/0.5ml
- one single dose solvent for Docetaxel vial of concentrate 1.5ml

**Docetaxel 80mg/2ml**
Each blister pack contains:
- one single dose Docetaxel vial of concentrate 80mg/2ml
- one single dose solvent for Docetaxel vial of concentrate 6ml

### 2. PRESENTATION

#### 2.1 Docetaxel 20mg/0.5ml vial

**Docetaxel 20mg/0.5ml concentrate for solution for infusion vial**
8ml clear glass Type I vial with a flip-off cap. This vial contains 0.5ml of a 40mg/ml solution of docetaxel in citric acid anhydrous, polysorbate 80 and ethanol absolute (fill volume: 25.2mg/0.63ml). This fill volume has been established during the development of Docetaxel to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and “dead-volume”. This overfill ensures that after dilution with the entire contents of the accompanying solvent for Docetaxel vial, there is a minimal extractable premix volume of 8ml containing 10mg/ml docetaxel which corresponds to the labelled amount of 80mg/2ml per vial.

#### 2.2 Solvent for Docetaxel 80mg/2ml vial

*Solvent vial: 15ml clear glass Type I vial with a flip-off cap.*
Solvent vial contains 6ml of a 9.53% w/w solution of ethanol absolute in water for injections (fill volume: 7.04ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel 80mg/2ml concentrate for solution for infusion vial ensures a premix concentration of 10mg/ml docetaxel.

### 3. RECOMMENDATIONS FOR THE SAFE HANDLING

Docetaxel is an antineoplastic agent and as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel solutions. The use of gloves is recommended. If Docetaxel concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Docetaxel concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.
2.2 Solvent for Docetaxel 20mg/0.5ml vial

Solvent vial: 8ml clear glass Type I vial with a flip-off cap. Solvent vial contains 1.5ml of a 9.53% w/w solution of ethanol absolute in water for injections (fill volume: 2.0ml). The addition of the entire contents of the solvent vial to the contents of the Docetaxel 20mg/0.5ml concentrate for solution for infusion vial ensures a premix concentration of 10mg/ml docetaxel.

2.1 Docetaxel 80mg/2ml vial

Docetaxel 80mg/2ml concentrate for solution for infusion vial: 15ml clear glass Type I vial with a flip-off cap. This vial contains 2ml of a 40mg/ml solution of docetaxel in citric acid anhydrous, polysorbate 80 and ethanol absolute (fill volume: 92.0mg/2.3ml). This fill volume has been established during the development.

4. PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

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

4.1.1. If the vials are stored under refrigeration, allow the required number of Docetaxel boxes to stand at room temperature for 5 minutes.

4.1.2. Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for Docetaxel vial by partially inverting the vial.
4.1.3. Inject the entire contents of the syringe into the corresponding Docetaxel vial.

4.1.4. Remove the syringe and needle and mix manually by repeated inversions for at least 120 seconds. Do not shake.

4.1.5. Allow the premix vial to stand for 3 minutes at room temperature and then check that the solution is homogenous and clear (foaming is normal even after 3 minutes due to the presence of polysorbate 80 in the formulation).

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

4.2 Preparation of the infusion solution

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

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

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

4.2.4. The Docetaxel infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.

4.2.5. As with all parenteral products, Docetaxel premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

5. SHELF LIFE

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

- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at about 25°C at normal lighting conditions, and 4 hours at 5°C ± 3°C protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6. DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 4
Labelling

Docetaxel 20mg/0.5ml Concentrate and Solvent for Solution for Infusion

Intravenous use

1x 20mg vial + Diluent

Cytotoxic

CAUTION: Dilution required with the entire contents of the solvent vial. Reconstitute premix solution requires further dilution prior to administration. See accompanying preparation guide.

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

Single-use vials - discard unused contents appropriately.

Each carton of Docetaxel 20mg/0.5ml concentrate and solvent for solution for infusion contain:

- one single dose vial concentrate
- one single dose vial solvent

Read the package leaflet before use.

Keep out of reach of children.

Do not store above 25°C

Store in original packaging in order to protect from light.

For storage conditions of the diluted medicinal product, see package leaflet.

1x20mg vial + Diluent

Cytotoxic

actavis

actavis

Parish, Bishop Mills

UK/H/1917/001-002/DC
PAR Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion

Dilute before use
Read the package leaflet before use.

PL 30306/0143

L18891SN-30

Docetaxel
20mg/0.5ml
Concentrate for Solution for Infusion
Intravenous use

Cytotoxic

EXP Batch

Solvent for
Docetaxel
20mg/0.5ml
9.53% (w/w) ethanol absolute in water for injections
1.5ml Vial
PL 30306/0143

EXP Batch
PAR Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion

UK/H/1917/001-002/DC

Docetaxel 80mg/2ml Concentrate and Solvent for Solution for Infusion

Intravenous use

1x 80mg vial + Diluent

Cytotoxic

Dilute before use
CAUTION: Dilution required with the entire contents of the solvent vial. Read the product information and follow the instructions for use. See accompanying preparation guide.

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

Single-use vials - discard unused contents appropriately.

Each carton of Docetaxel 80mg/2ml concentrate and solvent for solution for infusion contains:
- 48 cartons of Docetaxel 80mg/2ml concentrate and solvent for solution for infusion
- 1 vial of solvent for dilution

Fixed the package leaflet before use. Store out of reach and sight of children.

Do not store above 25°C

Store in original packaging in order to protect from light.

For storage conditions of the diluted medicinal product, see package leaflet.

Actavis, Barnstable, S50 8G4, UK
PAR Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion

Dilute before use
Read the package leaflet before use.
PL 30306/0144
L188945IN-30

Docetaxel
80mg/2ml
Concentrate for Solution for Infusion
Intravenous use

Solvent for
Docetaxel
80mg/2ml
9.53% (w/w) ethanol absolute in water for injections
6ml Vial
PL 30306/0144

Cytotoxic
EXP Batch

actavis
L188925IN-30
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion (PL 30306/0143-4; UK/H/1917/001-002/DC) could be approved.

These applications were submitted using the decentralised procedure, with the UK as reference member state (RMS), and Belgium, Cyprus, Greece, Iceland, Lithuania, Latvia, Malta, Romania and Slovenia as concerned member states (CMS). The products are prescription-only medicines for the treatment of different types of cancer.

These are abridged applications for Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Taxotere® 20mg and 80mg Concentrate and Solvent for Solution for Infusion (Aventis Pharma SA, France) which has been authorised in the EEA for over 10 years. Given that the results of appropriate non-clinical tests have been provided to support the applicant’s claim of pharmaceutical equivalence of the proposed products to the innovator product, the legal basis of the applications is considered valid.

These products contain the active substance docetaxel, which is a semisynthetic taxoid produced from the needles of the European yew tree. It is an antineoplastic drug belonging to the taxane group and is structurally and pharmacologically similar to paclitaxel. Docetaxel acts as a cytotoxic by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. It is used in the treatment of a wide range of malignancies, including breast cancer, non-small cell lung cancer, head and neck cancer, prostate cancer and gastric adenocarcinoma.

All non-clinical studies were conducted in accordance with Good Laboratory Practice (GLP).

No new clinical studies were conducted, which is acceptable given that the legal basis of the applications and that the applications cross-refer to products that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 12 April 2010. After a subsequent national phase, the licence was granted in the UK on 22 June 2010.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antineoplastic Agents (L01C D02)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Concentrate and Solvent for Solution for Infusion; 20mg/ml and 80mg/ml</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1917/001-002/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Belgium, Cyprus, Greece, Iceland, Lithuania, Latvia, Malta, Romania and Slovenia</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 30306/0143-4</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Actavis Group PTC ehf., Reykjavikurvegur 76-78, 220 Hafnarfjörður, Iceland</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

Active substance
INN: Docetaxel
Pharmacopeial name: Docetaxel
Chemical name: 2R, 3S-N-Carboxy-3-phenylisoserine, N-tert-butylester, 13-ester with 5beta, 20-epoxy-1,2 alpha 4, 7 beta, 10beta, 13 alpha-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate

Structure:

Molecular formula: C_{43}H_{53}NO_{14}
Molecular weight: 807.88 g/mol (anhydrous substance)
Appearance: A white to off-white powder, which is highly hygroscopic. At 25°C, docetaxel is freely soluble in ethanol and tetrahydrofuran, sparingly soluble in acetonitrile, soluble in methanol, acetone and ethyl acetate and insoluble in n-hexane and water.

Docetaxel was not the subject of a European Pharmacopoeia (Ph. Eur.) monograph at the time of initial assessment.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

Confirmation has been provided that the raw materials, intermediates and auxiliary agent used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications and certificates of analysis have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning plastic containers and closures for pharmaceutical use, and with legislation relating to primary packaging in contact with foodstuff.
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**Medicinal Product**

**Other Ingredients**
Other ingredients consist of the pharmaceutical excipients citric acid anhydrous, ethanol absolute and polysorbate 80 (in the concentrate vial) and ethanol absolute and water for injections (in the solvent vial). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**
The objective of the pharmaceutical development programme was to produce a concentrate and solvent for solution for infusion, containing either 20mg/0.5ml or 80mg/2ml, that could be considered a generic medicinal product of Taxotere® 20mg or 80mg Concentrate and Solvent for Solution for Infusion (Aventis Pharma SA, France).

A satisfactory account of the pharmaceutical development has been provided. It was noted that there are differences between the proposed generic medicinal products and their respective reference products by way of the additional excipients present. For this reason, additional studies were performed to: compare micelle size and distribution for the proposed versus reference products; to examine the influence of the drug product composition on docetaxel protein binding and to compare toxicokinetic profiles. These are discussed in Section III.2, Non-Clinical Aspects.

Comparative impurity profiles have been provided for both generic medicinal products and their respective reference products. Based on the data provided, the applicant’s Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion are considered equivalent to Taxotere® 20mg and 80mg Concentrate and Solvent for Infusion (Aventis Pharma SA, France).

**Manufacturing Process**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.
Container-Closure System
Both the concentrate and the solvent are presented in Type I clear glass vials, with a bromobutyl rubber stoppers and an aluminium/polypropylene seals. For the concentrate, the seal is green for the 20mg and red for the 80mg strength. One vial of concentrate and one vial of solvent are packed into a polystyrene tray, which is then packaged into a cardboard carton.

The Marketing Authorisation holder has committed to submit the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with parenteral products.

Stability of the product
Stability studies were performed in accordance with current guidelines, using batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months for the unopened vials with the storage conditions “Do not store above 25°C. Store in the original package in order to protect from light.”

Storage conditions of the reconstituted and the diluted medicinal product:
- Premix solution: The premix solution should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature (below 25°C). The premix solution is for single use only.
- Infusion solution: Chemical and physical in-use stability has been demonstrated for 4 hours at about 25°C and normal lighting conditions, and 4 hours at 5°C ± 3°C protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Please refer to the Summary of Product Characteristics information on safe handling and disposal of the product and contaminated materials.

Bioequivalence
Bioequivalence studies were not provided to support these applications.

The following non-clinical studies were performed to support the applicant’s claim of pharmaceutical equivalence with the reference products and are discussed in Section III.2, Non-Clinical Aspects:

- In vitro characterisation of micelles (Micelle study)
- Comparative Critical Micellar Concentration Study
- In vitro plasma protein binding study
- Comparative toxicokinetics study
Summary of Product Characteristics (SPC), Product Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable. Final text versions of the labelling and PIL have been provided.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the grant of marketing authorisations on quality grounds.
III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of docetaxel are well-known. However, it was noted that there are differences between the proposed generic medicinal products and their respective reference products by way of the additional excipients present. It is for this reason that additional studies have been performed to: compare micelle size and distribution for the proposed versus reference products; to examine the influence of the drug product compositions on docetaxel protein binding and to compare toxicokinetic profiles between products.

Micelle size and distribution
In vitro micelle size, size distribution and zeta potential were compared at various time-points during the shelf-life of both the proposed and reference products. The results demonstrated that both the proposed and reference products form micelles that are comparable in size, when diluted as instructed, and that the micelles are comparable between batches manufactured over time and do not change with storage, when stored to the recommended time and as instructed.

Comparative Critical Micellar Concentration
A further study to evaluate the self-assembling properties of the proposed and reference products used the determination of surface tension isotherms to measure the Critical Micellar Concentration (CMC) in different solvents. The results showed that the self-assembling properties of the surfactant are modified in the presence of electrolytes and organic molecules. Furthermore, the test and reference products exhibit similar properties in terms of the CMC for the solubilisation of the drug substance in infusion solutions.

In vitro plasma protein binding
Comparative in vitro protein binding of docetaxel was investigated in rats, dogs and humans. Plasma incubation samples at 1, 2.5, and 5 μg/ml were prepared from the test product (Docetaxel Actavis 20mg/0.5ml (40mg/ml)) and reference product (Taxotere 20mg (40mg/ml)). Results of this study are shown below:

### Comparative Docetaxel Protein Binding in Rat, Dog and Human plasma for Docetaxel Actavis (test) and Taxotere (reference)

<table>
<thead>
<tr>
<th></th>
<th>Rat</th>
<th>Dog</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Free fraction (mean ±SD)</td>
<td>% Bound Fraction (mean ±SD)</td>
<td>% Free Fraction (mean ±SD)</td>
</tr>
<tr>
<td>Docetaxel Actavis 40mg/ml</td>
<td>5.07 ± 0.206</td>
<td>94.93 ± 0.206</td>
<td>2.59 ± 0.144</td>
</tr>
<tr>
<td>Taxotere 40mg/ml</td>
<td>4.71 ± 0.328</td>
<td>95.29 ± 0.328</td>
<td>2.62 ± 0.187</td>
</tr>
</tbody>
</table>

SD = standard deviation

The results indicate that there were no significant differences between the test and reference products in terms of the protein binding of docetaxel. These data support the claim of equivalence of the proposed and reference products.
Comparative toxicokinetics

A repeat-dose toxicokinetic study was conducted in rats to qualify the levels of a novel impurity identified during the shelf-life of the proposed generic products. The pharmacokinetic results include two animal groups treated with the proposed product with or without an increased content of impurities. Pharmacokinetic parameters were determined as part of this impurity qualification study to separately compare in vivo pharmacokinetics of the test product (Docetaxel Actavis) and reference product (Taxotere) in order to support the claim of equivalence. The results of this study are shown below:

<table>
<thead>
<tr>
<th>Test article</th>
<th>Docetaxel Actavis with spiked impurity</th>
<th>Docetaxel Actavis without spiked impurity</th>
<th>Taxotere®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>1.25 mg/kg</td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL) Day 1</td>
<td>34.6</td>
<td>35.3</td>
<td>83.2</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-&lt;/sub&gt;&lt;sub&gt;last&lt;/sub&gt; (ng min/mL) Day 1</td>
<td>3940</td>
<td>1350</td>
<td>8510</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL) Day 2</td>
<td>38.5</td>
<td>36.6</td>
<td>83.3</td>
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<td>AUC&lt;sub&gt;0-&lt;/sub&gt;&lt;sub&gt;last&lt;/sub&gt; (ng min/mL) Day 2</td>
<td>3080</td>
<td>3300</td>
<td>7400</td>
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* - outlier value for Male 148 included in this value

This study showed that there were no major or consistent differences in the toxicological profiles of the test product (with or without increased impurity) versus the reference product.

To summarise, the additional studies show that:

1. The size, distribution and stability of the micelles formed in the infusion solutions of the proposed product are similar to those formed in solutions of the reference product.
2. Mean protein binding (free and bound fractions of docetaxel) are equivalent between samples treated with the proposed or reference products (as shown by the in vitro protein binding studies in rat, dog and human plasma).
3. No major differences in peak levels or systemic exposure of docetaxel were observed in an in vivo toxicokinetic study performed in rats.

The data provided support the claim that the proposed docetaxel products are pharmaceutically equivalent to their respective reference products.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the grant of marketing authorisations on non-clinical grounds.
III.3 CLINICAL ASPECTS

TOXICOLOGY
All new non-clinical studies conducted are discussed in the Section III.2, Non-Clinical Aspects.

CLINICAL PHARMACOLOGY
The clinical pharmacology of docetaxel is well-known. No new pharmacodynamic or pharmacokinetic data are supplied or required for these applications.

No bioequivalence studies are submitted. According to CHMP guidelines in force at the time of application, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98). However this product is a non-aqueous solution that is diluted in normal saline or 5% glucose prior to administration and no specific guidance is given. Pharmaceutical and non-clinical evidence provided by the applicant support the claim that the physico-chemical properties of these products and their respective reference products are equivalent. It is considered that no further clinical studies are required.

Efficacy
No new efficacy data are submitted with this application and none are required. The applicant has provided an acceptable review of clinical trials published in the literature confirming the efficacy of docetaxel.

Safety
No new safety data are submitted with these applications and none are required. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of docetaxel is well-known.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

Summary of Product Characteristics (SPC), Product Information Leaflet(PIL), Labels
The approved SPCs are satisfactory and consistent with those for the reference products.

The final PIL and labelling texts are satisfactory, and consistent with those for the reference products and with the approved SPC.

The Marketing Authorisation Holder (MAH) has committed to submit mock-ups of pack sizes to the regulatory authorities before marketing these commercially.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
Conclusion
There are no objections to the grant of marketing authorisations on clinical grounds.
IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Docetaxel Actavis 20mg/0.5ml and 80mg/2ml concentrate and solvent for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

NON-CLINICAL
The applicant has conducted an adequate programme of non-clinical studies to support the claim of equivalence between these products and their respective reference products. These non-clinical studies, as well as data to compare the physico-chemical properties of proposed and reference products, have shown that the proposed products can be considered generic medicinal products of Taxotere 20mg/0.5ml and 80mg/2ml Concentrate and Solvent for Infusion (Aventis Pharma SA, France).

EFFICACY
No new studies were submitted or required for these applications.

The results of appropriate non-clinical tests have been provided to support the applicant’s claim of pharmaceutical equivalence of the proposed products with the innovator product.

SAFETY
No new safety data are supplied or required for these generic applications. Docetaxel has a well-established side-effect profile.

PRODUCT LITERATURE
The approved SPCs are satisfactory and consistent with those for the reference products.

The final PIL and labelling texts are satisfactory and consistent with those for the reference products and with the approved SPCs.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Taxotere Concentrate and Solvent for Infusion (Aventis Pharma SA). Extensive clinical experience with docetaxel is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
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<th>Scope</th>
<th>Outcome</th>
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