Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

CETADO/DUCESOL/TAXCEUS 20MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

UK/H/1791-3/001/DC
UK Licence No: PL 24668/0147-9

CADUCEUS PHARMA LIMITED

LAY SUMMARY

On 2nd August 2010, the UK granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicines Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion (PL 24668/0147-9; UK/H/1791-3/001/DC).

Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion contains docetaxel. Docetaxel belongs to a group of anti-cancer medicines called taxoids.

Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion is used alone or in combination in the treatment of

- breast cancer
- special forms of lung cancer (non-small cell lung cancer)
- prostate cancer (used in combination only)
- gastric cancer (used in combination only)
- head and neck cancer (used in combination only).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of using Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations were granted.

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Module 1

Product Name	Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion
Type of Application	Generic hybrid, Article 10.3
Active Substance	Docetaxel
Form	Concentrate for solution for infusion
Strength	20mg/ml
MA Holder	Caduceus Pharma Ltd. 6th Floor, 94 Wigmore Street London W1U 3RF United Kingdom
Reference Member State (RMS)	UK
CMS	UK/H/1791/01/DC: Austria, Belgium, Denmark, Finland, Germany, Italy, the Netherlands, Spain, Sweden. UK/H/1792/01/DC: Austria, Belgium, Germany, Italy, the Netherlands, Spain. UK/H/1793/01/DC: Germany, Italy, Spain, the Netherlands.
Procedure Number	UK/H/1791-3/001/DC
End of Procedure	Day 160 – 14th July 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ducesol/Cetado/Taxceus 20mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose vial contains docetaxel 20mg/ml
Each 1ml single dose vial contains 20mg docetaxel
Each 4ml single dose vial contains 80mg docetaxel
Each 7ml single dose vial contains 140mg docetaxel
Excipient: Ethanol absolute 400mg/ml
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
The concentrate is a clear, pale yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Ducesol/Cetado/Taxceus in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node- positive breast cancer.
Ducesol/Cetado/Taxceus 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.

Ducesol/Cetado/Taxceus 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.

Ducesol/Cetado/Taxceus in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors over express HER2 and who previously have not received chemotherapy for metastatic disease.

Ducesol/Cetado/Taxceus 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

Ducesol/Cetado/Taxceus is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
Ducesol/Cetado/Taxceus 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

Ducesol/Cetado/Taxceus in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

Gastric Adenocarcinoma

Ducesol/Cetado/Taxceus 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

Ducesol/Cetado/Taxceus in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

4.2 Posology and method of administration

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

Recommended 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/m^2 administered 1-hour after doxorubicin 50mg/m^2 and cyclophosphamide 500mg/m^2 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/m^2 in monotherapy. In first-line treatment, docetaxel 75mg/m^2 is given in combination therapy with doxorubicin (50mg/m^2).

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

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

Non-small cell lung cancer

In chemotherapy naïve patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75mg/m^2 immediately followed by cisplatin 75mg/m^2 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/m^2. Prednisone or prednisolone 5mg orally twice daily is administered continuously (see section 5.1).

Gastric adenocarcinoma

The recommended dose of docetaxel is 75mg/m^2 as a 1 hour infusion, followed by cisplatin 75mg/m^2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750mg/m^2 per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion.
Treatment is repeated every three weeks. Patients must receive premedication with antiemetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of hematological toxicities (See also 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/m^2 as a 1 hour infusion followed by cisplatin 75mg/m^2 over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

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

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 ≥1,500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100mg/m^2 to 75mg/m^2 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/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is <25000 cells/mm^3, 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/m^2. For cisplatin dosage adjustments, see manufacturer's summary of product characteristics.

In combination with capecitabine

- For capecitabine dose modifications, see capecitabine summary of product characteristics.
- For patients developing the first appearance of a Grade 2 toxicity, which persists at the time of the next docetaxel/capecitabine treatment, delay treatment until resolved to Grade 0-1, and resume at 100% of the original dose.
- For patients developing the second appearance of a Grade 2 toxicity, or the first appearance of a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with docetaxel 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/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level >1,500

cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. Discontinue treatment if these toxicities persist. (See section 4.4).

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

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

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

In the pivotal SCCHN 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/m^2 (see sections 4.4 and 5.2). For those patients with serum bilirubin > ULN and/or ALT and AST >3.5 times the ULN associated with alkaline phosphatase >6 times the ULN, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

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

This medicinal product contains 400mg ethanol perml concentrate. This has to be taken into account in high-risk groups such as patients with liver disease.

Children and adolescents

Docetaxel is not recommended for use in children due to insufficient data on safety and/or efficacy.

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.
Patients with baseline neutrophil count of <1,500 cells/mm^3.
Patients with severe liver impairment (see sections 4.2 and 4.4).
Contraindications for other medicinal products also apply, when combined with docetaxel.

4.4 Special warnings and precautions for use

For breast and non-small cell lung cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 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 ≥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). Since Ducesol/Cetado/Taxceus contains ethanol (400mg ethanol per ml concentrate), consideration should be given to possible central nervous system and other effects.

Cardiac toxicity
Heart failure has been observed in patients receiving docetaxel in combination with trastuzumab, particularly following anthracycline (doxorubicin or epirubicin) - containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8).
When patients are candidates for treatment with docetaxel in combination with trastuzumab, they should undergo baseline cardiac assessment. Cardiac function should be further monitored during treatment (e.g. every three months) to help identify patients who may develop cardiac dysfunction. For more details see Summary of Product Characteristics of trastuzumab.

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

Ethanol
Ducesol/Cetado/Taxceus contains 400mg ethanol per ml concentrate. This may be harmful in patients suffering from alcoholism and should also be taken into consideration in children and high-risk groups such as patients with liver disease or other diseases affecting the central nervous system (e.g. epilepsy). The amount of alcohol in this medicinal product may alter the effects of other medicines.

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.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicinal products as concomitant therapy since there is a potential for a significant interaction. Docetaxel is highly protein bound (>95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medication has not been investigated formally, *in vitro* interactions with tightly protein-bound agents such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of docetaxel. In addition, dexamethasone did not affect protein binding of docetaxel. Docetaxel did not influence the binding of digitoxin.

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

Ducesol/Cetado/Taxceus contains 400mg ethanol per ml concentrate. In higher doses (7.5ml concentrate (150mg) contains 3g ethanol) the amount of alcohol 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 medicinal products, docetaxel may cause foetal harm when administered to pregnant women. Therefore, docetaxel must not be used during pregnancy unless clearly indicated.

Women of childbearing 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.
Ducesol/Cetado/Taxceus contains 400mg ethanol per ml concentrate. In higher doses (7.5ml concentrate (150mg docetaxel) contains 3g ethanol) the amount of alcohol 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 (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000) not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The most commonly reported adverse reactions of docetaxel alone are: neutropenia (which was reversible and not cumulative; the median day to nadir was 7 days and the median duration of severe neutropenia (<500 cells/mm^3) was 7 days), 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 disorder*s
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 3kg 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 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:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10	**Uncommon adverse reactions** ≥1/1000, <1/100
Investigations		G3/4 Blood bilirubin increased (<5%); G3/4 Blood alkaline phosphatase increased (<4%); G3/4 AST increased (<3%); G3/4 ALT increased (<2%)	
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Blood and the lymphatic system disorders	Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%); Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%); Peripheral motor neuropathy (G3/4: 4%) Dysgeusia (severe 0.07%)		
Respiratory, thoracic and mediastinal disorders	Dyspnoea (severe 2.7%)		
Gastrointestinal disorders	Stomatitis (G3/4: 5.3%); Diarrhoea (G3/4: 4%); Nausea (G3/4: 4%); Vomiting (G3/4: 3%)	Constipation (severe 0.2%); Abdominal pain (severe 1%); Gastrointestinal Haemorrhage (severe 0.3%)	Oesophagitis (severe: 0.4%)
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 5.9%); Nail disorders (severe 2.6%)		
Musculoskeletal, connective tissue and bone disorders	Myalgia (severe 1.4%)	Arthralgia	
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Vascular disorders		Hypotension; Hypertension; Haemorrhage	
General disorders and administration site conditions	Fluid retention (severe: 6.5%) Asthenia (severe 11.2%); Pain	Infusion site reaction; Non-cardiac chest pain (severe 0.4%)	
Immune system disorders	Hypersensitivity (G3/4: 5.3%)		

Blood and Lymphatic system disorders
Rare: bleeding episodes associated with grade 3/4 thrombocytopenia
Nervous system disorders
Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 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/m^2 and the median time to fluid retention reversibility was 16.4 weeks (range 0 to 42 weeks). The onset of moderate and severe retention is delayed (median cumulative dose: 818.9mg/m^2) in patients with premedication compared with patients without premedication (median cumulative dose: 489.7mg/m^2); however, it has been reported in some patients during the early courses of therapy.

Docetaxel 75mg/m² single agent:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10
Investigations		G3/4 Blood bilirubin increased (<2%)
Cardiac disorders		Arrhythmia (no severe);
Blood and the lymphatic system disorders	Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Gastrointestinal disorders	Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhea (G3/4: 1.7%)	Constipation
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 0.8%)	Nail disorders (severe 0.8%)
Musculoskeletal, connective tissue and bone disorders		Myalgia
Metabolism and nutrition disorders	Anorexia	
Infections and infestations	Infections (G3/4: 5%)	
Vascular disorders		Hypotension
General disorders and administration site conditions	Asthenia (severe 12.4%); Fluid retention (severe 0.8%); Pain	
Immune system disorders		Hypersensitivity (no severe)

Docetaxel 75mg/m² in combination with doxorubicin:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10	**Uncommon adverse reactions** ≥1/1,000, <1/100
Investigations		G3/4 Blood bilirubin increased (<2.5%); G3/4 Blood alkaline phosphatase increased (<2.5%)	G3/4 AST increased (<1%); G3/4 ALT increased (<1%)
Cardiac disorders		Cardiac failure; Arrhythmia (no severe)	
Blood and the lymphatic system disorders	Neutropenia (G4: 91.7%); Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)		
Nervous system disorders	Peripheral sensory neuropathy (G3: 0.4%)	Peripheral motor neuropathy (G3/4: 0.4%)	
Gastrointestinal disorders	Nausea (G3/4: 5%); Stomatitis (G3/4: 7.8%); Diarrhoea (G3/4: 6.2%);		

	Vomiting (G3/4: 5%); Constipation		
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe 0.4%); Skin reaction (no severe)		
Musculoskeletal, connective tissue and bone disorders		Myalgia	
Metabolism and nutrition disorders		Anorexia	
Infections and infestations	Infection (G3/4: 7.8%)		
Vascular disorders			Hypotension
General disorders and administration site conditions	Asthenia (severe 8.1%); Fluid retention (severe 1.2%); Pain	Infusion site reaction	
Immune system disorders		Hypersensitivity (G3/4: 1.2%)	

Docetaxel 75mg/m² in combination with cisplatin:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10	**Uncommon adverse reactions** ≥1/1,000, <1/100
Investigations		G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased (1.3%)	G3/4 AST increased (0.5%); G3/4 Blood alkaline phosphatase increased (0.3%)
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Blood and the lymphatic system disorders	Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%); Thrombocytopenia (G4:0.5%)	Febrile neutropenia	
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%); Peripheral motor neuropathy (G3/4: 2%)		
Gastrointestinal disorders	Nausea (G3/4: 9.6%); Vomiting (G3/4: 7.6%); Diarrhoea (G3/4: 6.4%); Stomatitis (G3/4: 2%)	Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe 0.7%); Skin reaction (G3/4: 0.2%)		
Musculoskeletal, connective tissue and bone disorders	Myalgia (severe 0.5%)		
Metabolism and nutrition disorders	Anorexia		
Infections and infestations	Infection (G3/4: 5.7%)		
Vascular disorders		Hypotension (G3/4: 0.7%)	

General disorders and administration site conditions	Asthenia (severe 9.9%); Fluid retention (severe 0.7%); Fever (G3/4: 1.2%)	Infusion site reaction; Pain	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		

Docetaxel 100mg/m² in combination with trastuzumab:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10
Investigations	Weight increased	
Cardiac disorders		Cardiac failure
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%); Febrile neutropenia (includes neutropenia associated with fever and antibiotic use) or neutropenic sepsis	
Nervous system disorders	Paresthesia; Headache; Dysgeusia; Hypoaesthesia	
Eye disorders	Lacrimation increased; Conjunctivitis	
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, connective tissue and bone disorders	Myalgia; Arthralgia; Pain in extremity; Bone pain; Back pain	
Metabolism and nutrition disorders	Anorexia	
Vascular disorders	Lymphoedema	
General disorders and administration site conditions	Asthenia; Oedema peripheral; Pyrexia; Fatigue; Mucosal inflammation; Pain; Influenza like illness; Chest pain; Chills	Lethargy
Psychiatric disorders	Insomnia	

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/m^2 is known to result in neutropenia in 97% of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

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%)

Blood and the lymphatic system disorders	Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Nervous system disorders	Dysgeusia (G3/4: <1%); Paraesthesia (G3/4: <1%)	Dizziness; Headache (G3/4: <1%); Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%)	Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%)
Gastrointestinal disorders	Stomatitis (G3/4: 18%); 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, connective tissue and bone disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4: <1%); Back pain (G3/4: 1%);
Metabolism and nutrition disorders	Anorexia (G3/4: 1%); Decreased appetite	Dehydration (G3/4: 2%);
Infections and infestations		Oral candidiasis (G3/4: <1%)
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4: 5%); Oedema peripheral (G3/4: 1%);	Lethargy; Pain

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

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10
Cardiac disorders		Cardiac left ventricular function decrease (G3/4: 0.3%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%); Anaemia (G3/4: 4.9%)	Thrombocytopenia; (G3/4: 0.6%); Febrile neutropenia
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G3/4: 0.6%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%); Dyspnoea (G3/4: 0.6%); Cough (G3/4: 0%)
Gastrointestinal disorders	Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (no severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal, connective tissue and bone disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	

Infections and infestations	Infection (G3/4: 3.3%)	
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)	
Immune system disorders		Hypersensitivity (G3/4: 0.6%)

Docetaxel 75mg/m² in combination with doxorubicin and cyclophosphamide:

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10	**Uncommon adverse reactions** ≥1/1,000, <1/100
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		
Nervous system disorders	Dysgeusia (G3/4: 0.7%); Peripheral sensory neuropathy (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%); Neurocortical (G3/4: 0.3%); Neurocerebellar (G3/4: 0.1%)	Syncope (G3/4: 0%)
Eye disorders		Lacrimation disorder (G3/4: 0.1%); Conjunctivitis (G3/4: 0.3%)	
Respiratory, thoracic and mediastinal disorders		Cough (G3/4: 0%)	
Gastrointestinal disorders	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%)	Abdominal pain (G3/4: 0.5%)	Colitis/enteritis/ large intestine perforation
Skin and subcutaneous tissue disorders	Alopecia; Skin toxicity (G3/4: 0.7%); Nail disorders (G3/4: 0.4%)		
Musculoskeletal, connective tissue and bone disorders	Myalgia (G3/4: 0.8%); Arthralgia (G3/4: 0.4%)		
Metabolism and nutrition disorders	Anorexia (G3/4: 2.2%)		
Infections and infestations	Infection (G3/4: 3.2%); Neutropenic infection. There were no septic deaths.		
Vascular disorders	Vasodilatation (G3/4: 0.9%)	Hypotension (G3/4: 0%)	Phlebitis (G3/4: 0%); Lymphoedema (G3/4: 0%)
General disorders and administration site conditions	Asthenia (G3/4: 11%); Fever (G3/4: 1.2%); Oedema peripheral (G3/4: 0.4%)		
Immune system disorders	Hypersensitivity (G3/4: 1.1%)		
Reproductive system and	Amenorrhoea		

breast disorders			

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:

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

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)

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

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA System Organ classes	**Very common adverse reactions** ≥1/10	**Common adverse reactions** ≥1/100, <1/10	**Uncommon adverse reactions** ≥1/1,000, <1/100
Investigations	Weight decreased		Weight increased
Cardiac disorders		Arrhythmia (G3/4:2.0%)	Ischemia myocardial

Blood and the lymphatic system disorders	Neutropenia (G3/4:83.5%) Anemia (G3/4:12.4%) Thrombocytopenia (G3/4:4.0%) Febrile neutropenia		
Nervous system disorders	Dysgeusia/Parosmia (G3/4:0.4%); Peripheral sensory neuropathy (G3/4:1.2%)	Dizziness (G3/4:2.0%); Peripheral motor neuropathy (G3/4:0.4%)	
Eye disorders		Lacrimation increased	Conjunctivitis
Ear and labyrinth disorders	Hearing impaired (G3/4:1.2%)		
Gastrointestinal disorders	Nausea (G3/4: 13.9%); Stomatitis (G3/4:20.7%); Vomiting (G3/4:8.4%); Diarrhoea (G3/4: 6.8%); Esophagitis/dysphagia/ odynophagia (G3/4:12.0%); Constipation (G3/4:0.4%)	Dyspepsia (G3/4:0.8%); Gastrointestinal pain (G3/4: 1.2%); Gastrointestinal haemorrhage (G3/4:0.4%)	
Skin and subcutaneous tissue disorders	Alopecia (G3/4:4.0%); Rash pruritic	Dry skin; Desquamation	
Musculoskeletal, connective tissue and bone disorders		Myalgia (G3/4:0.4%)	
Metabolism and nutrition disorders	Anorexia (G3/4:12.0%)		
Infections and infestations	Infection (G3/4:3.6%)	Neutropenic infection	
Neoplasms benign and malignant (including cysts and polyps)		Cancer pain (G3/4: 1.2%)	
Vascular disorders			Venous disorder
General disorders and administration site conditions	Lethargy (G3/4:4.0%) Pyrexia (G3/4:3.6%) Fluid retention (G3/4:1.2) Oedema (G3/4:1.2%)		
Immune system disorders			Hypersensitivity

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 medicinal product.

Eye Disorders
Very rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during infusion of the medicinal product and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion. Cases of lacrimation with or

without conjunctivitis, as cases of lacrimal duct obstruction resulting in excessive tearing have been rarely reported.

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

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.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare cases of acute myeloid leukaemia and myelodysplastic syndrome have been reported in association with docetaxel when used in combination with other chemotherapy agents and/or radiotherapy.

Vascular disorders
Venous thromboembolic events have rarely been reported.

General disorders and administration site conditions
Radiation recall phenomena have rarely been reported.
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 ≥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 medicinal products 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:

		Disease Free Survival			**Overall Survival**		
Patient subset	**Number of patients**	**Hazard ratio***	**95% CI**	**P=**	**Hazard ratio***	**95% CI**	**P=**
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.70	0.53-0.91	0.008
1-3	467	0.61	0.46-0.82	0.0009	0.45	0.29-0.70	0.0002
4+	278	0.83	0.63-1.08	0.17	0.94	0.66-1.33	0.72

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

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

Parameter	Docetaxel plus trastuzumab[1] n=92	Docetaxel[1] n=94
Response rate (95% CI)	61% (50-71)	34% (25-45)
Median Duration of response (months)	11.4	5.1

(95% CI)	(9.2-15.0)	(4.4-6.2)
Median TTP (months) (95% CI)	10.6 (7.6-12.9)	5.7 (5.0-6.5)
Median Survival (months) (95% CI)	30.5[2] (26.8-ne)	22.1[2] (17.6-28.9)

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

Docetaxel in combination with capecitabine
Data from one multicenter, randomised, controlled phase III clinical 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/m^2 as a 1 hour intravenous infusion every 3 weeks) and capecitabine (1250mg/m^2 twice daily for 2 weeks followed by 1-week rest period). 256 patients were randomised to treatment with docetaxel alone (100mg/ m^2 as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the docetaxel +capecitabine combination arm (p=0.0126). Median survival was 442 days (docetaxel + capecitabine) vs. 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.6% (docetaxel + capecitabine) vs. 29.7% (docetaxel alone); p = 0.0058. Time to progressive disease was superior in the docetaxel + capecitabine combination arm (p <0.0001). The median time to progression was 186 days (docetaxel + capecitabine) vs. 128 days (docetaxel alone).

Non-Small Cell Lung Cancer
Patients previously treated with chemotherapy with or without radiotherapy
In a phase III study, in previously treated patients, time to progression (12.3 weeks versus 7 weeks) and overall survival were significantly longer for docetaxel at 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 analgesic (p <0.01), non-morphinic analgesics (p <0.01), other disease related medications (p=0.06) and radiotherapy (p <0.01) in patients treated with docetaxel at 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/m^2 as a 1 hour infusion immediately followed by cisplatin (Cis) 75mg/ m^2 over 30-60 minutes every 3 weeks, docetaxel 75mg/ m^2 as a 1 hour infusion in combination with carboplatin (AUC 6mg/ml•min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25mg/ m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100mg/ m^2 administered on day 1 of cycles repeated every 4 weeks.
Survival data, median time to progression and response rates for two arms of the study are illustrated in the following table:

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

Overall Response Rate (%):	31.6	24.5	Treatment difference: 7.1% [95% CI: 0.7; 13.5]

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

Secondary end-points included change of pain, global rating of quality of life by EuroQoL-5D, Lung Cancer Symptom Scale, and changes in Karnosfky performance status. Results on these end-points were supportive of the primary end-points results.
For docetaxel/carboplatin combination, neither equivalent nor non-inferior efficacy could be proven compared to the reference treatment combination VCis.

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

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

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

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

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/m^2 on day 1) in combination with cisplatin (C) (75mg/m^2 on day 1) and 5-fluorouracil (F)

(750mg/m^2 per day for 5 days) or cisplatin (100mg/m^2 on day 1) and 5-fluorouracil (1000mg/m^2 per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The median number of cycles administered per patient was 6 (with a range of 1-16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p=0.0004) in favor of the TCF arm. Overall survival was also significantly longer (p=0.0201) in favor of the TCF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarized in the following table:

Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

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

*Unstratified logrank test

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

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

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

Head and neck cancer

- Induction chemotherapy followed by radiotherapy (TAX323)

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

regimens of radiation therapy (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week). A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy. Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 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 n=177**	**Cis+5-FU n=181**
Median progression free survival (months) (95%CI)	11.4 (10.1-14.0)	8.3 (7.4-9.1)
Adjusted Hazard ratio (95%CI) *p-value	0.70 (0.55-0.89) 0.0042	
Median survival (months) (95%CI)	18.6 (15.7-24.0)	14.5 (11.6-18.7)
Hazard ratio (95%CI) **p-value	0.72 (0.56-0.93) 0.0128	
Best overall response to chemotherapy (%)(95%CI)	67.8 (60.4-74.6)	53.6 (46.0-61.0)
***p-value	0.006	
Best overall response to study treatment [chemotherapy +/- radiotherapy] (%) (95%CI)	72.3 (65.1-78.8)	58.6 (51.0-65.8)
***p-value	0.006	
Median duration of response to chemotherapy ± radiotherapy (months) (95%CI)	n=128 15.7 (13.4-24.6)	n=106 11.7 (10.2-17.4)
Hazard ratio (95%CI) **p-value	0.72 (0.52-0.99) 0.0457	

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

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

Clinical benefit parameters
The performance status scale, for head and neck (PSS-HN) subscales designed to measure understandability of speech, ability to eat in public, and normalcy of diet, was significantly in favor of TPF as compared to PF.
Median time to first deterioration of WHO performance status was significantly longer in the TPF arm compared to PF. Pain intensity score improved during treatment in both groups indicating adequate pain management.

- Induction chemotherapy followed by chemoradiotherapy (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)

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

A Hazard ratio of less than 1 favors docetaxel + 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/m^2 in Phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the α, β and γ phases of 4 min, 36 min

and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100mg/m^2 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/m^2 and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.
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 ≥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 medicinal product.
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.
Undesirable effects on the testis observed in rodent toxicity studies suggest that docetaxel may impair male fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Povidone
Polysorbate 80
Ethanol absolute

6.2 Incompatibilities

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

6.3 Shelf life

Vials as packed for sale:
24 months
After dilution:
The diluted solution should be used immediately after preparation. However, the physical and chemical stability of the diluted solution (0.74mg/ml) in the recommended solutions for infusion (50mg/ml (5%)

glucose solution for infusion and 9mg/ml (0.9%) sodium chloride solution for infusion) has been demonstrated for 8 hours at about 25°C and normal lighting conditions.

6.4 Special precautions for storage

Store below 25°C
Store in the original package in order to protect from light
For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

Colourless glass vial (type I) closed with a bromobutyl rubber stopper (type I) sealed with aluminium cap with polypropylene disc. Vial will be packed with or without a protective plastic overwrap.
Pack sizes:
1 x 1ml single dose vial
1 x 4ml single dose vial
1 x 7ml single dose vial
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Ducesol/Cetado/Taxceus is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Ducesol/Cetado/Taxceus solutions. Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of such preparations. Refer to local cytotoxic guidelines before commencing. The use of gloves is recommended. If Ducesol/Cetado/Taxceus concentrate or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Ducesol/Cetado/Taxceus concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation of the solution for infusion
More than one vial of Ducesol/Cetado/Taxceus 20mg/ml concentrate for solution for infusion may be necessary to obtain the required dose for individual patients. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding volume of 20mg/ml docetaxel from the appropriate number of vials using graduated syringes fitted with a needle. For example, a dose of 140mg docetaxel would require 7ml of Ducesol/Cetado/Taxceus 20mg/ml concentrate for solution for infusion.

For doses below 192mg of docetaxel, inject the required volume of Ducesol/Cetado/Taxceus 20mg/ml concentrate for solution for infusion into a 250ml infusion bag or bottle containing either 250ml of 50mg/ml (5%) glucose solution for infusion or 9mg/ml (0.9%) sodium chloride solution for infusion. For doses exceeding 192mg of docetaxel more than 250ml of the infusion solution is required, as the maximum concentration of docetaxel is 0.74mg per ml of infusion solution.
Mix the infusion bag or bottle manually using a rocking motion. The diluted solution should be used within 8 hours and should be aseptically administered as a 1-hour infusion at room temperature and normal lighting conditions.

Administration
For instructions on administration see Section 4.2.
As with all parenteral products, this medicinal product should be visually inspected prior to use and solutions containing a precipitate should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 24668/0147, 8 and 9

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/08/2010

10 DATE OF REVISION OF THE TEXT

02/08/2010

Module 3

Please note that the leaflet shown below is for PL 24668/0147 only.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ducesol 20 mg/ml concentrate for solution for infusion

docetaxel

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.

In this leaflet:

1. WHAT DUCESOL IS AND WHAT IT IS USED FOR

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

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

2. BEFORE YOU USE DUCESOL

Do not use Ducesol if
• you are allergic (hypersensitive) to docetaxel or any other ingredients of Ducesol.
• the number of white blood cells is too low.
• you have a severe liver disease.

Take special care with Ducesol

Before each treatment with Ducesol, you will have blood tests to check that you have enough blood cells and sufficient liver function to receive Ducesol. 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 Ducesol 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 Ducesol in particular allergic reactions and fluid retention (swelling of the hands, feet, legs or weight gain).

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

This medicinal product contains alcohol and may be harmful for those suffering from alcoholism and should be taken into account in high-risk groups such as patients with liver disease or epilepsy. In case any of the above conditions apply to you, discuss it with your doctor before the medicinal product is given to you.

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 Ducesol or the other medicine may not work as well as expected and you may be more likely to get a side effect.

Pregnancy

Ask your doctor for advice before being given any medicine.

Ducesol 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 contraceptive during therapy, because Ducesol 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 Ducesol 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 Ducesol.

Driving and using machines

There is no reason why you cannot drive between courses of Ducesol except if you feel dizzy or are unsure of yourself. In higher doses (7.5 ml concentrate (150 mg) contains 3 g ethanol) the amount of alcohol may impair your ability to drive or use machines.

Important information about some of the ingredients of Ducesol
This medicinal product contains 400 mg ethanol (alcohol) per ml concentrate. Harmful for those suffering from alcoholism. To be taken into account if you are pregnant or if you are a breast-feeding woman, in children and in high-risk groups such as patients with liver disease or epilepsy.
In higher doses (7.5 ml concentrate (150 mg) contains 3 g ethanol) the amount of alcohol may alter the effects of other medicines and impair your ability to drive or use machines.

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

3. HOW TO USE DUCESOL

Ducesol 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 (m^2) and will determine the dose you should receive.

Method and route of administration

Ducesol will be given by infusion into one of your veins. 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 Ducesol. 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, Ducesol 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 Ducesol alone are: decrease in the number of red blood cells or white blood cells, alopecia, nausea, vomiting, sores in the mouth, diarrhea and tiredness.

The severity of adverse events of Ducesol may be increased when Ducesol 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 Ducesol the following may occur, and the frequency may vary with the combinations of drugs that are received:

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 diarrhea, 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

Common (experienced in less than 1 in 10 but more than 1 in 100 patients)
• oral candidiasis
• dehydration
• dizziness
• hearing impaired
• decrease in blood pressure; irregular or rapid heart beat
• 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 DUCESOL

Keep out of the reach and sight of children.

Ducesol should not be used after the expiry date shown on the carton and vial.

Store below 25°C.
Store in the original package in order to protect from light.

The diluted solution should be used immediately after preparation. If not used immedialtely the in-use storage times and conditions are the responsibility of the user and would not normally be longer than 8 hours at room temperature (about 25°C) including the one hour infusion.
Dispose any unused product or waste material in accorbance with local requirements.

6. FURTHER INFORMATION

What Ducesol contains
- The active substance is docetaxel. Each ml of docetaxel solution contains 20 mg of docetaxel anhydrous.
- The other ingredients are citric acid anhydrous, povidone, ethanol absolute and polysorbate 80.

What Ducesol looks like and contents of the pack:
Ducesol concentrate for solution for infusion is a clear, pale yellow solution.

Pack sizes:
1 x 1 ml single dose vial
1 x 4 ml single dose vial
1 x 7 ml single dose vial

Not all pack sizes may be marketed

Marketing Authorisation Holder

Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

Manufacturer

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

This medicinal product is authorised in the Member States of the EEA under the following names:

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

Ducesol 20 mg/ml concentrate for solution for infusion

Instructions on use

Ducesol is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Ducesol solutions. Cytotoxic agents should be prepared for administration only by personnel who have been trained in the safe handling of such preparations. Refer to local cytotoxic guidelines before commencing. The use of gloves is recommended. If Ducesol concentrate or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If Ducesol concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation of the solution for infusion
More than one vial of Ducesol 20 mg/ml concentrate for solution for infusion may be necessary to obtain the required dose for individual patients. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding volume of 20 mg/ml docetaxel from the appropriate number of vials using graduated syringes fitted with a needle. For example, a dose of 140 mg docetaxel would require 7 ml of Ducesol 20 mg/ml concentrate for solution for infusion.

For doses below 192 mg of docetaxel, inject the required volume of Ducesol 20 mg/ml concentrate for solution for infusion into a 250 ml infusion bag or bottle containing either 250 ml of 50 mg/ml (5%) glucose solution for infusion or 9 mg/ml (0.9%) sodium chloride solution for infusion. For doses exceeding 192 mg of docetaxel more than 250 ml of the infusion solution is required, as the maximum concentration of docetaxel is 0.74 mg per ml of infusion solution.

Mix the infusion bag or bottle manually using a rocking motion. The diluted solution should be used within 8 hours and should be aseptically administered as a 1-hour infusion at room temperature and normal lighting conditions.

As with all parenteral products, this medicinal product should be visually inspected prior to use and solutions containing a precipitate should be discarded.

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

Storage after dilution
The diluted solution should be used immediately after preparation. However, the physical and chemical stability of the diluted solution (0.74 mg/ ml) in the recommended solutions for infusion (50 mg/ml (5%) glucose solution for infusion and 9 mg/ml (0.9%) sodium chloride solution for infusion) has been demonstrated for 8 hours at about 25°C and normal lighting conditions.

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

Module 4
Labelling

Please note that the labelling shown is for PL 24668/0147 only.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ducesol 20 mg/ml concentrate for solution for infusion

docetaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of concentrate contains 20 mg of docetaxel.

One vial of 1 ml of concentrate contains 20 mg docetaxel.
One vial of 4 ml of concentrate contains 80 mg docetaxel.
One vial of 7 ml of concentrate contains 140 mg docetaxel.

3. LIST OF EXCIPIENTS

Contains citric acid anhydrous, povidone, polysorbate 80, ethanol absolute.

4. PHARMACEUTICAL FORM AND CONTENTS

1 x 20 mg/1 ml single dose vial
1 x 80 mg/4 ml single dose vial
1 x 140 mg/7 ml single dose vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Must be diluted before use.
For intravenous use as infusion, after dilution.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic agent

8. EXPIRY DATE

EXP
The diluted medicinal product should be used immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 25°C
Store in the original package in order to protect from light.
Refer to the package leaflet for storage conditions after dilution.

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

Discard unused contents appropriately

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Ltd.
6th Floor, 94 Wigmore Street
London W1U 3RF
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0147

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

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

Ducesol 20 mg/ml concentrate for solution for infusion
docetaxel
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
For infusion after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg/1 ml single dose vial
80 mg/4 ml single dose vial
140 mg/7 ml single dose vial

6. OTHER

Cytotoxic agent

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria (UK/H/1791-2 only), Belgium (UK/H/1791-2 only), Denmark (UK/H/1791 only), Finland (UK/H/1791 only), Germany, Italy, the Netherlands, Spain and Sweden (UK/H/1791 only) and the UK considered that the applications for Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion could be approved. The products are prescription only medicines (POM) and are indicated for the following:

- **Breast cancer**

Adjuvant treatment of operable node- positive breast cancer (in combination with doxorubicin and cyclophosphamide).

Locally advanced or metastatic breast cancer (in combination with doxorubicin for the treatment of patients with who have not previously received cytotoxic therapy for this condition).

Locally advanced or metastatic breast cancer (as monotherapy or in combination with capecitabine after failure of cytotoxic chemotherapy).

Locally advanced or metastatic breast cancer

Metastatic breast cancer (in combination with trastuzumab for patients whose tumors over express HER2 and who have not received chemotherapy for metastatic disease).

- **Non-small cell lung cancer**

Locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

Unresectable, locally advanced or metastatic non-small cell lung cancer (in combination with cisplatin in patients who have not previously received chemotherapy).

- **Prostate cancer**

Hormone refractory metastatic prostate cancer (in combination with prednisone or prednisolone).

- **Gastric Adenocarcinoma**

Metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction (in combination with cisplatin and 5-fluorouracil in patients who have not received prior chemotherapy for metastatic disease).

- **Head and neck cancer**

Locally advanced squamous cell carcinoma of the head and neck (in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment).

These applications for Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion are submitted as abridged applications according to Article 10.3 of Directive 2001/83/EC, claiming to be generic hybrid medicinal products to Taxotere 20mg concentrate and solvent for infusion, first authorised in the EEA to Aventis Pharma S.A. in November 1995.

Docetaxel is a semi synthetic taxane manufactured from a taxane precursor derived from the needles of the European yew tree *Taxus baccata.*

Docetaxel acts by promoting the assembly of microtubules and prevent their depolymerisation, thus interfering with a number of normal cellular functions. The microtubule assembly is stable and dysfunctional, leading to disruption of the normal microtubule dynamics that is required for cell division and vital processes during interphase.

In addition to the detailed review of the non-clinical properties of docetaxel in the open literature, the applicant has submitted comparative studies designed to detect similarities and differences between Docetaxel 20 mg/ml and Taxotere in terms of efficacy, protein binding and toxicity in non-clinical models.
These studies have been reported and are listed as follows:

- Efficacy Evaluation of Docetaxel Actavis and Taxotere Against MX-1 Human Mammary Carcinoma Xenografts.
- Efficacy Evaluation of Docetaxel Actavis and Taxotere Against PC-3 Human Prostate Carcinoma Xenografts.
- Comparative Determination of the Effect of Formulation on the Plasma Protein Binding of Docetaxel Actavis and Taxotere in Rat, Dog, and Human Plasma.
- Intravenous (Infusion) Preliminary Study in the Rat.
- Cyclical Intravenous (Infusion) Comparative Study in the Rat.
- Maximum Tolerated Dose Determination for Docetaxel Actavis in Non-Tumor Bearing Outbred Nude Mice.

No new clinical studies were conducted, which is acceptable given the legal basis of the applications and that the applications cross-refer to products that have been licensed for over 10 years. Since adequate quality and non-clinical data were provided to support these applications, bioequivalence studies were not required.

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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting a

Risk Management Plan (RMP).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Cetado/Ducesol/Taxceus 20mg/ml concentrate for Solution for Infusion
Name(s) of the active substance(s) (INN)	Docetaxel
Pharmacotherapeutic classification (ATC code)	Antineoplastic agents (L01CD 02)
Pharmaceutical form and strength(s)	20mg/ml Concentrate for Solution for Infusion
Reference numbers for the Decentralised Procedure	UK/H/1791-3/001/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/1791/01/DC: Austria, Belgium, Denmark, Finland, Germany, Italy, the Netherlands, Spain, Sweden. UK/H/1792/01/DC: Austria, Belgium, Germany, Italy, the Netherlands, Spain. UK/H/1793/01/DC: Germany, Italy, Spain, the Netherlands.
Marketing Authorisation Number(s)	PL 24668/0147-9
Name and address of the authorisation holder	Caduceus Pharma Ltd. 6th Floor, 94 Wigmore Street London W1U 3RF United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

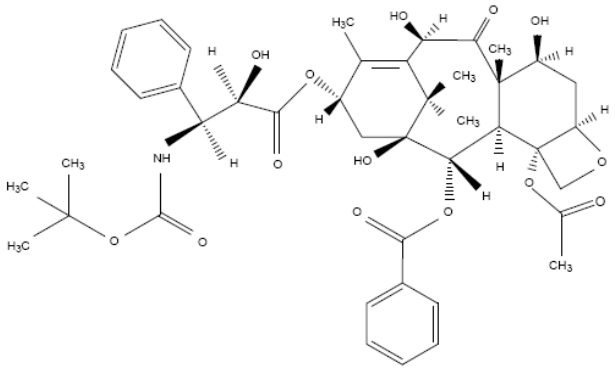
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur 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

Structural formula:



Molecular formula: $C_{43}H_{53}NO_{14}$

Appearance: white to off-white powder.

Solubility: freely soluble in ethanol and tetrahydrofuran, sparingly soluble in acetonitrile, soluble in methanol, acetone and ethyl acetate and insoluble in n-hexane and water.

Molecular weight: 807.88

Docetaxel complies with in-house specifications which are in-line with those in the European Pharmacopoeia monograph for docetaxel trihydrate.

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 specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance, with suitable test methods and limits. 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 specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

The other ingredients are the pharmaceutical excipients citric acid anhydrous, povidone, polysorbate 80 and ethanol absolute.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Taxotere 20mg concentrate and solvent for infusion, first authorised in the EEA to Aventis Pharma S.A. in November 1995.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Taxotere 20mg concentrate and solvent for infusion.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with three industrial-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

The product is packaged in a type I colourless glass vial closed with a type I bromobutyl rubber stopper sealed with aluminium cap with polypropylene disc. Vial will be packed with or without a protective plastic overwrap.

The product will be available in the following pack sizes:
1 x 1ml single dose vial
1 x 4ml single dose vial
1 x 7ml single dose vial

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24

months for an unopened product with storage conditions "Store below 25 ^{o}C" and "Store in the original package in order to protect from light".

After the solution has been diluted, it should be used immediately after preparation. However, the physical and chemical stability of the diluted solution (0.74mg/ml) in the recommended solutions for infusion (50mg/ml (5%) glucose solution for infusion and 9mg/ml (0.9%) sodium chloride solution for infusion) has been demonstrated for 8 hours at about 25°C and under normal lighting conditions.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for the PILs for these products. The results indicate that the PILs are 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 they contain.

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
The grant of these Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of docetaxel are well-known. However, it has been noted that there are differences between the proposed generic medicinal products and their respective reference product in the additional excipients present. It is for this reason that additional studies have been performed to compare efficacy, protein binding and toxicity in non-clinical models between products.

Efficacy

To determine the efficacy of Docetaxel 20 mg/ml Concentrate for solution for infusion, compared to Taxotere, established MX-1 human mammary carcinoma xenografts at a dose of docetaxel 20 mg/kg. Docetaxel 20 mg/ml and Taxotere were administered intravenously every fourth day for three treatments to female athymic (nu/nu) mice.

Treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg was active and produced Day 20 T/C (median tumour mass of the treated group divided by the median tumour mass of the control group x 100) values of 0%, and tumour growth delays of >38.3 days. There were 100% complete regressions and the animals remained tumour-free at study termination. Bioanalytical analysis of plasma for both compounds on the final day of dosing confirmed similar plasma concentrations for both test articles.

The results showed that treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg in terms of docetaxel content resulted in essentially identical anti-cancer activity against MX-1 human mammary carcinoma xenografts.

A further study to evaluate the anti-cancer activity of Docetaxel 20 mg/ml compared to Taxotere against established PC-3 human prostate xenografts at a dose of 20 mg/kg of the active ingredient, docetaxel, in male outbred athymic (nu/nu) mice. Docetaxel 20 mg/ml and Taxotere were administered intravenously every four days for three treatments.

Treatment with Docetaxel 20 mg/ml or Taxotere, at 20 mg/kg, was curative. It produced a Day 36 T/C value of 0%, and a tumour growth delay of >25.8 days. Treatment also produced 100% complete regressions, with all animals remaining tumour-free at study termination. Bioanalytical analysis of plasma for both compounds on the final day of dosing confirmed similar plasma concentrations of docetaxel for both test articles.

The results showed that treatment with either Docetaxel 20 mg/ml or Taxotere at 20 mg/kg in terms of docetaxel content resulted in identical anti-cancer activity against PC-3 human prostate xenografts.

Protein-binding

To determine the effect of different formulations on the degree (%) of protein binding of docetaxel, in rat, dog and human plasma in vitro, plasma protein binding determinations were made using the equilibrium dialysis technique, and samples analysed.
For the main protein binding experiments, plasma incubation samples at 1, 2.5, and 5 µg/mL were prepared in rat, dog and human plasma from five formulations of docetaxel (including the test formulation).
The time for the dialysis process to reach equilibrium when each docetaxel concentration was added to assay buffer was similar for each formulation.

The binding of docetaxel to proteins in rat, dog, and human plasma was determined, and, that

within each species, there were no significant differences between the test formulation and the reference formulation.

Toxicology

To determine the maximum tolerated dose of Docetaxel 20mg/ml, upon intravenous administration every four days for three injections, a study using the substance against a vehicle control, which has the same composition as the drug product but contained no active substance was conducted. Mice were dosed according to their individual body weight on the day of the treatment (0.2ml/20g). Primary endpoints for this study were mortality, weight loss, clinical signs, skin lesions, and necropsy observations. All animals were observed for clinical signs at least once daily. Individual body weights were recorded three times weekly. Treatment-related weight loss in excess of 20% is generally considered unacceptably toxic. In this report, a dosage level is described as tolerated if treatment-related weight loss (during and two weeks after treatment) is <20% and mortality during this period is ≤10%. The clinical signs observed during the study and the maximum tolerated dose are similar with effects previously described for Taxotere.

In another study which was a preliminary study to determine the dose of docetaxel to use in the main study (see below), 2 male and 2 female rats were dosed once only, at a dose level of 10mg/kg docetaxel, and were then observed for 3 weeks to allow observation for delayed toxicity. All animals were observed frequently on the day of dosing, then daily for any visible signs of reaction to treatment. Body weights and food consumption were measured weekly and the animals were subjected to macroscopic necropsy at the end of the observation period. There were no unscheduled deaths or toxicologically significant clinical changes. Bodyweight gain and food consumption values were lower for both sexes over Days 1 to 8 (the week immediately following treatment) than over Days 8 to 15 and Days 15 to 22.
No abnormalities were noted at necropsy.
It was considered that 10 mg/kg docetaxel would be a suitable high dose level for the main comparative study described below.

The objective of this study was to compare the toxicity and pharmacokinetics of Docetaxel 20 mg/ml and Taxotere solutions following intravenous administration by cyclical infusion in the rat.
Table no.1 summarises the design of the study and dose levels of the active ingredient, docetaxel:

Table no. 1

Product and docetaxel dose level mg/kg (mg/m2)	Number of toxicity study animals Males	Females	Number of toxicokinetic satellite study animals Males	Females
Control (DOCETAXEL 20 mg/ml Vehicle)	10 (5)	10 (5)	3	3
DOCETAXEL 20 mg/ml 2.5 (15)	10	10	9	9
DOCETAXEL 20 mg/ml 5.0 (30)	10	10	9	9
DOCETAXEL 20 mg/ml	10 (5)	10 (5)	9	9
Control (Taxotere® Vehicle)	10 (5)	10 (5)	3	3

Taxotere® 2.5 (15)	10	10	9	9
Taxotere® 5.0 (30)	10	10	9	9
Taxotere® 10.0 (60)	10 (5)	10 (5)	9	9

The toxicity study animals were sacrificed and subjected to necropsy 6 weeks after the initial dose. Animals identified in parenthesis were allocated to a 3 week recovery period following the end of the main study and necropsied 9 weeks after the initial dose.

For each subset, the dose levels examined were 0, 2.5, 5.0 and 10.0 mg/kg (equivalent to 0, 15, 30 and 60 mg/m^2) of docetaxel active ingredient. Animals were dosed twice by a 1 hour intravenous infusion at a nominal rate of 13.5 mL/kg/hr, once on Day 1 and once on Day 22. Two cycles of treatment at a three weekly interval were considered sufficient. The low dose of 2.5 mg/kg is a nominal clinical dose (approximately equivalent to 100 mg/m^2 to patients), the high dose was expected to induce toxicity, and reduced body weight gain and food consumption were observed in the preliminary study.
All formulations were accurately prepared (within 10 % of nominal) and no docetaxel was found in control samples.

Six unscheduled deaths occurred during the study, none of which were considered to be related to treatment with either Docetaxel 20 mg/ml or Taxotere. There were no toxicologically significant adverse clinical signs.

Plasma concentrations of docetaxel were measurable up to 8 hours post-dose for all plasma samples for the higher two dose levels and for the majority of plasma samples for the 2.5 mg/kg dose level. This indicates almost continuous exposure of the rats to docetaxel up to 8 hours post-dose at all dose levels. The apparent Tmax generally occurred at 5 minutes post-dose, however this is an underestimate of the actual Tmax. Plasma concentrations of docetaxel declined with mean terminal half-lives, where calculable, in the range 140 minutes to 216 minutes.

Peak levels and systemic exposure increased from the 2.5 mg/kg to the 5 mg/kg dose levels in an approximately dose proportional manner. However, the increase in systemic exposure data showed an approximate 1.5-fold increase greater than the dose level increase for both Day 1 and Day 22 data for the 10.0 mg/kg dose groups. These parameters are compared in table no. 2.

Table no. 2

Test article	Docetaxel Actavis						Taxotere®					
Dose level	2.5 mg/kg		5 mg/kg		10 mg/kg		2.5 mg/kg		5 mg/kg		10 mg/kg	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Cmax (ng/mL) Day 1	53.2	53.4	173	141	540	737	66.9	47.4	155	191	1130	477
AUC0-8 (ng.mins/mL) Day 1	5680	4580	11500	9920	33800	33800	5610	5360	11100	12200	38500	31000

Cmax (ng/mL) Day 22	68.7	66.7	206	123	689	416	74.1	56.3	182	119	470	385
AUC0-8 (ng.mins/mL) Day 22	7660	4100	16200	9250	44800	26200	5770	5030	16000	12400	40800	27300

Generally, there appeared to be no consistent differences between sexes for the peak levels of docetaxel or the systemic exposure on Day 1. On Day 22, the male rats showed a small but consistent increase (less than 2-fold) in both peak levels and the systemic exposure of docetaxel. Where calculable, clearance and volume of distribution were slightly higher in females, consistent with the lower levels of exposure in the females on Day 22. The extent of systemic exposure following a second administration was similar compared to a single administration. Clearance and volume of distribution values, where calculable, were generally similar following the second dose. Overall, there was little accumulation potential of docetaxel following a second administration.

There were neither major nor consistent differences for the peak levels or the systemic exposure of docetaxel following dosing with either Docetaxel 20 mg/ml or Taxotere.
It is concluded that the toxicological profile based on evaluation of body weight gain, food consumption, ophthalmic examination, haematology and bone marrow smears, clinical chemistry, urinalysis, organ weights, gross and histopathology and toxicokinetic profiles of Docetaxel 20 mg/ml and Taxotere, following 2 cycles of intravenous infusion dosing, 3 weeks apart, at dose levels of 2.5, 5.0 or 10.0 mg/kg docetaxel, were comparable. Administration of either product resulted in changes consistent with the known toxicity of the active ingredient docetaxel.

This study showed that there were no major or consistent differences in the toxicological profiles of the test product versus the reference product.

These studies show:

1. Treatment with Docetaxel 20 mg/ml and Taxotere at 20mg/kg in terms of docetaxel content resulted in identical anti-cancer activity against both the MX-1 and PC-3 xenografts following intravenous administration every four days for three treatments.
2. The clinical signs observed in the study and the maximum tolerated dose were similar to those previously described for Taxotere.
3. The developed drug product pharmacokinetics properties were essentially comparable with reference product in terms of toxicokinetics.

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

The non-clinical overview has been written by an appropriately qualified physician and is adequate.

A suitable justification has been provided for non-submission of an Environmental Risk Assessment.

There are no objections to the approval of Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 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.

However, the product contains micelles and micelle solutions for IV administration may be regarded as 'complex' solutions and therefore do not automatically qualify for a biowaiver. To address this issue, the quality/physicochemical properties of the proposed product were shown to be comparable with the reference product by the provision of adequate quality and non-clinical data. Therefore, no further clinical studies were required.

3. Post marketing experience

Docetaxel has a well-recognised efficacy and an acceptable level of safety in the indications approved for Taxotere 20mg concentrate and solvent for infusion, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the Marketing Authorisations is supported.

4. Benefit-Risk assessment

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with docetaxel is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of the Marketing Authorisations for Cetado/Ducesol/Taxceus 20mg/ml concentrate for solution for infusion is recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Cetado/Ducesol/Taxceus 20mg/ml concentrate 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 benefit/risk balance.

NON-CLINICAL

Due to differences between the proposed generic medicinal products and the reference product with regards to additional excipients, additional studies have been performed to compare efficacy, protein binding and toxicity between products in non-clinical models between products. These studies support the claim that the products are equivalent to the reference product.

CLINICAL

No bioequivalence studies have been performed and none are considered required for these applications, since adequate quality and non-clinical data have been provided.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with docetaxel is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome