Docetaxel STADA® concentrate for solution for infusion 20mg / ml

COMPOSITION:
Each single dose vial contains docetaxel 20 mg/ml

Each 1 ml single dose vial contains 20 mg docetaxel
Each 4 ml single dose vial contains 80 mg docetaxel
Each 7 ml single dose vial contains 140 mg docetaxel

Excipients: Ethanol absolute 400 mg/ml, Citric acid anhydrous, Povidone, Polysorbate 80

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

INDICATIONS
Breast cancer
Docetaxel STADA® is indicated for the treatment of patients with locally advanced or metastatic breast carcinoma.

Non-small cell lung cancer
Docetaxel STADA® is indicated for the treatment of patients with locally advanced or metastatic non- small cell lung cancer.

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

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

Head and neck cancer
Docetaxel STADA® 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.

POSOLOGY AND METHOD OF ADMINISTRATION

Recommended dosage
For breast, non-small cell lung, gastric, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, unless contraindicated, can be used (see section on Special warnings and Precautions for use).
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 8 mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion (see section Special warnings and Precautions for use).

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

Breast cancer
For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dosage of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 60 mg/m^2 is given in combination therapy with doxorubicin (50 mg/ m^2).

In combination with trastuzumab the recommended dose of docetaxel is 100 mg/ m^2 every three weeks, with trastuzumab administered weekly. In the pivotal 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 package insert .

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

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

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

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

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

  For cisplatin and 5-fluorouracil dose modifications, see the corresponding package insert.

  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 count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

  In combination with cisplatin
  For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 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 65 mg/m^2. For cisplatin dosage adjustments, see manufacturer's package insert.

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

  For trastuzumab dose modifications, see trastuzumab package insert

  In combination with cisplatin and 5-fluorouracil:
  If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs

despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/ m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist. (See section on special warnings and precautions for use).

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

Toxicity	**Dosage adjustment**
Diarrhea grade 3	First episode: reduce 5-FU dose by 20%. Second episode: then reduce docetaxel dose by 20%.
Diarrhea 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 package insert.

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 100 mg/m² as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75 mg/m^2 (see sections Special warnings and precautions for use and Pharmacokinetic properties). 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 400 mg ethanol per ml 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 package insert)

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 Method of administration and Special warnings and precautions for use).
Contraindications for other medicinal products also apply, when combined with docetaxel.

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

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 Method of administration).

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 on Method of administration).

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 section on Method of administration and Undesirable effects).

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 on Method of administration).

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

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

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

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 on Method of administration). Since Docetaxel Stada contains ethanol (400 mg 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 on Undesirable effects).

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 package insert of trastuzumab.

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

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 on Fertility, pregnancy and lactation).

The concomitant use of docetaxel with strong CYP3A4 inihibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see Interactions with other medicinal products and other forms of interaction)

Ethanol
Docetaxel Stada contains 400 mg ethanol per ml concentrate. This may be harmful in patients suffering from alcoholism and should also be taken into consideration in pregnant or breast- feeding women, 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.

The amount of alcohol in this medicinal product may impair the patient's ability to drive or use machines.

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

at rates ≥ 10% higher in patients who were 75 years of age or greater versus less than 65 years.

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

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 ciclosporin, ketoconazole, erythromycin. 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.

In case of combination with CYP3A4 inhibitors, the occurrence of docetaxel adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor (see Special warnings and precautions for use). In pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to significant decrease in docetaxel clearance by 49%.

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

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.

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 monotheraphy.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
There is no information on the use of docetaxel in pregnant women. Docetaxel has been shown to be both embryotoxic and foetotoxic in rabbits and rats, and to reduce fertility in rats. As with

other cytotoxic medicinal products, docetaxel may cause foetal harm when administered to pregnant women. Therefore, docetaxel must not be used during pregnancy unless clearly indicated.

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

An effective method of contraception should be used during 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.

Fertility:
In non-clinical studies, docetaxel has genotoxic effects and may alter male fertility (see Preclinical safety data). 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed. The amount of ethanol in Docetaxel STADA® may impair the ability to drive or use machines (see Special warnings and precautions for use)

UNDESIRABLE EFFECTS
Summary of the safety profile for all indications
The adverse reactions considered to be possibly or probably related to the administration of docetaxel have been obtained in:

- 1312 and 121 patients who received 100 mg/m^2 and 75 mg/m^2 of docetaxel as a single agent respectively
- 406 patients who received docetaxel in combination with cisplatin.
- 255 patients who received docetaxel in combination with capecitabine.
- 332 patients who received docetaxel in combination with prednisone or prednisolone (clinically important treatment related adverse events are presented).
- 300 gastric adenocarcinoma patients (221 patients in 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).
- 258 patients who received docetaxel in combination with doxorubicin.

These reactions were described using the NCI Common Toxicity Criteria (grade 3 = G3; grade 3 - 4 = G3/4; grade 4 = G4), the COSTART and the MedDRA terms. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
Within the 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 capecitabine, the most frequent treatment-related undesirable effects (≥ 5%) reported in a phase III study in breast cancer patients failing anthracycline treatment are presented (see capecitabine package insert).

The following adverse reactions are frequently observed with docetaxel:

Immune system disorders
Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of docetaxel and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills.

Severe reactions were characterized by hypotension and/or bronchospasm or generalized rash/erythema (see Special warnings and precaution for use)

Nervous system disorders
The development of severe peripheral neurotoxicity requires a reduction of dose (see Posology and method of administration and Special warnings and precautions for use). Mild to moderate neuro-sensory signs are characterized by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

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

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

Tabulated list of adverse reactions in breast cancer for Docetaxel STADA® single agent

MedDRA System Organ Classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infections (G3/4: 5.7%; including sepsis and pneumonia, fatal in 1.7%)	Infection associated with G4 neutropenia (G3/4: 4.6%)	
Blood and lymphatic system disorders	Neutropenia (G4: 76.4%); Anaemia (G3/4: 8.9%); Febrile neutropenia	Thrombocytopenia (G4: 0.2%)	
Immune system disorders	Hypersensitivity (G3/4: 5.3%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 4.1%); Peripheral motor neuropathy (G3/4: 4%); Dysgeusia (severe: 0.07%)		
Cardiac disorders		Arrhythmia (G3/4: 0.7%)	Cardiac failure
Vascular disorders		Hypotension; Hypertension; Haemorrhage	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (severe: 2.7%)		
Gastrointestinal disorders	Stomatitis (G3/4: 5.3%); Diarrhoea (G3/4: 4%); Nausea (G3/4: 4%); Vomiting (G3/4: 3%)	Constipation (severe: 0.2%); Abdominal pain (severe: 1%); Gastrointestinal haemorrhage (severe: 0.3%)	Oesophagitis (severe: 0.4%)
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 5.9%); Nail disorders (severe: 2.6%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe: 1.4%)	Arthralgia	

General disorders and administration site conditions	Fluid retention (severe: 6.5%); Asthenia (severe: 11.2%); Pain	Infusion site reaction; Non-cardiac chest pain (severe: 0.4%)	
Investigations		G3/4 Blood bilirubin increased (< 5%); G3/4 Blood alkaline phosphatase increased (< 4%); G3/4 AST increased (< 3%); G3/4 ALT increased (< 2%)	

Description of selected adverse reactions in breast cancer for Docetaxel STADA® single agent

Blood and lymphatic system disorders

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

Nervous system disorders

Reversibility data are available among 35.3% of patients who developed neurotoxicity following docetaxel treatment at 100 mg/m² as single agent. The events were spontaneously reversible within 3 months.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

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

Tabulated list of adverse reactions in non-small cell lung cancer for Docetaxel STADA® single agent

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Infections (G3/4: 5%)	
Blood and lymphatic system disorders	Neutropenia (G4: 54.2%); Anaemia (G3/4: 10.8%); Thrombocytopenia (G4: 1.7%)	Febrile neutropenia
Immune system disorders		Hypersensitivity (no severe)
Metabolism and nutrition disorders	Anorexia	

Nervous system disorders	Peripheral sensory europathy (G3/4: 0.8%)	Peripheral motor neuropathy (G3/4: 2.5%)
Cardiac disorders		Arrhythmia (no severe)
Vascular disorders		Hypotension
Gastrointestinal disorders	Nausea (G3/4: 3.3%); Stomatitis (G3/4: 1.7%); Vomiting (G3/4: 0.8%); Diarrhoea (G3/4: 1.7%)	Constipation
Skin and subcutaneous tissue disorders	Alopecia; Skin reaction (G3/4: 0.8%)	Nail disorders (severe: 0.8%)
Musculoskeletal and connective tissue disorders		Myalgia
General disorders and administration site conditions	Asthenia (severe: 12.4%); Fluid retention (severe: 0.8%); Pain	
Investigations		G3/4 Blood bilirubin increased (< 2%)

Tabulated list of adverse reactions in breast cancer for Docetaxel STADA® in combination with doxorubicin

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 7.8%)		
Blood and lymphatic system disorders	Neutropenia (G4: 91.7%) Anaemia (G3/4: 9.4%); Febrile neutropenia; Thrombocytopenia (G4: 0.8%)		
Immune system disorders		Hypersensitivity (G3/4: 1.2%)	
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders	Peripheral sensory Neuropathy (G3: 0.4%)	Peripheral motor Neuropathy (G3/4: 0.4%)	
Cardiac disorders		Cardiac failure; Arrhythmia (no severe)	
Vascular disorders			Hypotension

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

Tabulated list of adverse reactions in non-small cell lung cancer for Docetaxel STADA® in combination with cisplatin

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4: 5.7%)		
Blood and lymphatic system disorders	Neutropenia (G4: 51.5%); Anaemia (G3/4: 6.9%) Thrombocytopenia (G4: 0.5%)	Febrile neutropenia	
Immune system disorders	Hypersensitivity (G3/4: 2.5%)		
Metabolism and nutrition disorders	Anorexia		
Nervous system disorders	Peripheral sensory neuropathy (G3: 3.7%) Peripheral motor neuropathy (G3/4: 2%);		
Cardiac disorders		Arrythmia (G3/4: 0.7%)	Cardiac failure

Vascular disorders		Hypotension (G3/4: 0.7%)	
Gastrointestinal disorders	Nausea (G3/4: 9.6%) Vomiting (G3/4: 7.6%) Diarrhoea (G3/4: 6.4%) Stomatitis (G3/4: 2%)	Constipation	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (severe: 0.7%); Skin reaction (G3/4: 0.2%)		
Musculoskeletal and connective tissue disorders	Myalgia (severe 0.5%)		
General disorders and administration site conditions	Asthenia (severe: 9.9%); Fluid retention (severe:0.7%); Fever (G3/4: 1.2%)	Infusion site reaction: Pain	
Investigations		G3/4 Blood bilirubin increased (2.1%); G3/4 ALT increased 1.3%)	G3/4 AST increased (0.5%); G3/4 Blood alkaline Phosphatase increased (0.3%)

Tabulated list of adverse reactions in breast cancer for Docetaxel STADA® in combination with capecitabine

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations		Oral candidiasis (G3/4: <1%)
Blood and the lymphatic system disorders	Neutropenia (G3/4: 63%); Anaemia (G3/4: 10%)	Thrombocytopenia (G3/4: 3%)
Metabolism and nutrition disorders	Anorexia (G3/4: 1%); Decreased appetite	Dehydration (G3/4: 2%);
Nervous system disorders	Dysgeusia (G3/4: <1%); Paraesthesia (G3/4: <1%)	Dizziness; Headache (G3/4: <1%); Neuropathy peripheral
Eye disorders	Lacrimation increased	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain (G3/4: 2%)	Dyspnoea (G3/4: 1%); Cough (G3/4: <1%); Epistaxis (G3/4: <1%)

Gastrointestinal disorders	Stomatitis (G3/4: 18%); Diarrhoea (G3/4: 14%); Nausea (G3/4: 6%); Vomiting (G3/4: 4%); Constipation (G3/4: 1%); Abdominal pain (G3/4:2%); Dyspepsia	Abdominal pain upper; Dry mouth
Skin and subcutaneous tissue disorders	Hand-foot syndrome (G3/4: 24%) Alopecia (G3/4: 6%); Nail disorders (G3/4: 2%)	Dermatitis; Rash erythematous (G3/4:<1%); Nail discolouration; Onycholysis (G3/4: 1%)
Musculoskeletal and connective tissue disorders	Myalgia (G3/4: 2%); Arthralgia (G3/4: 1%)	Pain in extremity (G3/4:<1%); Back pain (G3/4: 1%);
General disorders and administration site conditions	Asthenia (G3/4: 3%); Pyrexia (G3/4: 1%); Fatigue/ weakness (G3/4:5%); Oedema peripheral (G3/4:1%);	Lethargy; Pain
Investigations		Weight decreased; G3/4 Blood bilirubin increased (9%)

Tabulated list of adverse reactions in prostate cancer for Docetaxel STADA® in combination with prednisone or prednisolone

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**
Infections and infestations	Infection (G3/4: 3.3%)	
Blood and the lymphatic system disorders	Neutropenia (G3/4: 32%); Anaemia (G3/4: 4.9%)	Thrombocytopenia; (G3/4: 0.6%); Febrile neutropenia
Immune system disorders		Hypersensitivity (G3/4: 0.6%)
Metabolism and nutrition disorders	Anorexia (G3/4: 0.6%)	
Nervous system disorders	Peripheral sensory neuropathy (G3/4: 1.2%); Dysgeusia (G3/4: 0%)	Peripheral motor neuropathy (G3/4: 0%)
Eye disorders		Lacrimation increased (G3/4: 0.6%)
Cardiac disorders		Cardiac left ventricular function decrease (G3/4:0.3%)
Respiratory, thoracic and mediastinal disorders		Epistaxis (G3/4: 0%); Dyspnoea (G3/4: 0.6%); Cough (G3/4: 0%)

Gastrointestinal disorders	Nausea (G3/4: 2.4%); Diarrhoea (G3/4: 1.2%); Stomatitis/Pharyngitis (G3/4: 0.9%); Vomiting (G3/4: 1.2%)	
Skin and subcutaneous tissue disorders	Alopecia; Nail disorders (no severe)	Exfoliative rash (G3/4: 0.3%)
Musculoskeletal and connective tissue bone disorders		Arthralgia (G3/4: 0.3%); Myalgia (G3/4: 0.3%)
General disorders and administration site conditions	Fatigue (G3/4: 3.9%); Fluid retention (severe 0.6%)	

Tabulated list of adverse reactions in gastric adenocarcinoma cancer for Docetaxel STADA® in combination with cisplatin and 5-fluorouracil

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

Description of selected adverse reactions in gastric adenocarcinoma cancer for Docetaxel STADA® in combination with cisplatin and 5-fluorouracil

Blood and lymphatic system disorders

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

Tabulated list of adverse reactions in head and neck cancer for Docetaxel STADA® in combination with cisplatin and 5-fluorouracil

- Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4:6.3%) Neutropenic infection		
Neoplasms benign and malignant (including cysts and polyps)		Cancer pain (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	
Immune system disorders		Hypersensitivity (no severe)	
Metabolism and nutrition disorders	Anorexia (G3/4:0.6%)		
Nervous system disorders	Dysgeusia/Parosmia Peripheral sensory neuropathy (G3/4:0.6%)	Dizziness	
Eye disorders		Lacrimation increased Conjunctivitis	
Ear and labyrinth disorders		Hearing impaired	
Cardiac disorders		Myocardial ischemia (G3/4:1.7%)	Arrhythmia (G3/4:0.6%)
Vascular disorders		Venous disorder (G3/4:0.6%)	

Gastrointestinal disorders	Nausea (G3/4:0.6%) Stomatitis (G3/4;4.0%) 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%)	
General disorders and administration site conditions	Lethargy (G3/4:3.4%) Pyrexia (G3/4:0.6%) Fluid retention Oedema		
Investigations		Weight increased	

- Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA System Organ classes	**Very common adverse reactions**	**Common adverse reactions**	**Uncommon adverse reactions**
Infections and infestations	Infection (G3/4:3.6%)	Neutropenic infection	
Neoplasms benign and malignant and unspecified (including cysts and polyps)		Cancer pain (G3/4: 1.2%)	
Blood and the lymphatic system Disorders	Neutropenia (G3/4:83.5%) Anemia (G3/4:12.4%) Thrombocytopenia (G3/4:4.0%) Febrile neutropenia		
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Anorexia (G3/4:12.0%)		

Nervous system disorders	Dysgeusia/Parosmia (G3/4:0.4%); Peripheral sensory neuropathy (G3/4:1.2%)	Dizziness (G3/4:2.0%); Peripheral motor neuropathy (G3/4:0.4%)	
Eye disorders		Lacrimation increased	Conjunctivitis
Ear and labyrinth disorders	Hearing impaired (G3/4:1.2%)		
Cardiac disorders		Arrhythmia (G3/4:2.0%)	Ischemia myocardial
Vascular disorders			Venous disorder
Gastrointestinal disorders	Nausea (G3/4: 13.9%); Stomatitis (G3/4:20.7%); Vomiting (G3/4:8.4%); Diarrhea (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%)	
General disorders and administration site conditions	Lethargy (G3/4:4.0%) Pyrexia (G3/4:3.6%) Fluid retention (G3/4:1.2%) Oedema (G3/4:1.2%)		
Investigations	Weight decreased		Weight increased

Post-marketing experience

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

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

Blood and lymphatic system disorders

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

Immune system disorders

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

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

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

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

Cardiac disorders
Rare cases of myocardial infarction have been reported.

Vascular disorders
Venous thromboembolic events have rarely been reported.

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

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

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

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

Renal and urinary disorders
Renal insufficiency and renal failure have been reported. In about 20% of these cases there were no risk factors for acute renal failure such as concomitant nephrotoxic medicinal products and gastrointestinal disorders.

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

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

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group: Taxanes, ATC Code: L01CD02

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

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

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

Clinical efficacy and safety
Breast cancer

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

In alkylating-failure patients, docetaxel was compared to doxorubicin (75 mg/m² every 3 weeks).

Without affecting overall survival time (docetaxel 15 months vs. doxorubicin 14 months, p = 0.38) or time to progression (docetaxel 27 weeks vs. doxorubicin 23 weeks, p = 0.54), docetaxel

increased response rate (52% vs. 37%, p = 0.01) and shortened time to response (12 weeks vs. 23 weeks, p = 0.007). Three docetaxel patients (2%) discontinued the treatment due to fluid retention, whereas 15 doxorubicin patients (9%) discontinued due to cardiac toxicity (three cases of fatal congestive heart failure).

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

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

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

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

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

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

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

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

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

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

Docetaxel *in combination with platinum agents in chemotherapy-naive patients*
In a phase III study, 1218 patients with unresectable stage IIIB or IV NSCLC, with KPS of 70% or greater, and who did not receive previous chemotherapy for this condition, were randomised to either docetaxel (T) 75 mg/m² as a 1 hour infusion immediately followed by cisplatin (Cis) 75 mg/m² over 30-60 minutes every 3 weeks (TCis), docetaxel 75 mg/m² as a 1 hour infusion in combination with carboplatin (AUC 6 mg/ml.min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25 mg/m² administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100 mg/m² administered on day 1 of cycles repeated every 4 weeks (VCis).

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

	TCis n=408	VCis N=404	Statistical analysis
Overall survival (Primary end-point): Median survival (months)	11.3	10.1	Hazard Ratio: 1.122 [97.2% CI: 0.937; 1.342]*
1-year Survival (%)	46	41	Treatment difference: 5.4% [95% CI: -1.1; 12.0]
2-year Survival (%)	21	14	Treatment difference:

			6.2% [95% CI: 0.2; 12.3]
Median time to progression (weeks):	22.0	23.0	Hazard Ratio: 1.032 [95% CI: 0.876; 1.216]
Overall response rate (%):	31.6	24.5	Treatment difference: 7.1% [95% CI: 0.7; 13.5]

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

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

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

Prostate cancer

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

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

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

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

Endpoint	Docetaxel every 3 weeks	Docetaxel every week	Mitoxantrone every 3 weeks
Number of patients	335	334	337
Median survival (months)	18.9	17.4	16.5
95% CI	(17.0-21.2)	(15.7-19.0)	(14.4-18.6)
Hazard ratio	0.761	0.912	--
95% CI	(0.619-0.936)	(0.747-1.113)	--
p-value+*	0.0094	0.3624	--
Number of patients	291	282	300
PSA** response rate (%)	45.4	47.9	31.7
95% CI	(39.5-51.3)	(41.9-53.9)	(26.4-37.3)
p-value*	0.0005	<0.0001	--

Number of patients	153	154	157
Pain response rate (%)	34.6	31.2	21.7
95% CI	(27.1-42.7)	(24.0-39.1)	(15.5-28.9)
p-value*	0.0107	0.0798	--
Number of patients	141	134	137
Tumour response rate (%)	12.1	8.2	6.6
95% CI	(7.2-18.6)	(4.2-14.2)	(3.0-12.1)
p-value*	0.1112	0.5853	--

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

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

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

Gastric adenocarcinoma
A multicenter, open-label, randomized study was conducted to evaluate the safety and efficacy of docetaxel for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had not received prior chemotherapy for metastatic disease. A total of 445 patients with KPS > 70 were treated with either docetaxel (T) (75 mg/m² on day 1) in combination with cisplatin (C) (75 mg/ m² on day 1) and 5-fluorouracil (F) (750 mg/m² per day for 5 days) or cisplatin (100 mg/m² on day 1) and 5-fluorouracil (1000 mg/m² per day for 5 days). The length of a treatment cycle was 3 weeks for the TCF arm and 4 weeks for the CF arm. The median number of cycles administered per patient was 6 (with a range of 1- 16) for the TCF arm compared to 4 (with a range of 1-12) for the CF arm. Time to progression (TTP) was the primary endpoint. The risk reduction of progression was 32.1% and was associated with a significantly longer TTP (p = 0.0004) in favor of the TCF arm. Overall survival was also significantly longer (p = 0.0201) in favor of the TCF arm with a risk reduction of mortality of 22.7%. Efficacy results are summarized in the following table:

Efficacy of docetaxel in the treatment of patients with gastric adenocarcinoma

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	36.7	25.4

(CP+PR) (%)		
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 favour of the TCF arm. Patients treated with TCF had a longer time to 5% definitive deterioration of global health status on the QLQ-C30 questionnaire (p = 0.0121) and a longer time to definitive worsening of Karnofsky performance status (p = 0.0088) compared to patients treated with CF.

Head and neck cancer

- Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicenter, open-label, randomized study (TAX323). In this study, 358 patients with inoperable locally advanced SCCHN, and WHO performance status 0 or 1, were randomized to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75 mg/m² followed by cisplatin (P) 75 mg/m² followed by 5-fluorouracil (F) 750 mg/m² per day as a continuous infusion for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (TPF/RT). Patients on the comparator arm received cisplatin (P) 100 mg/m² followed by 5-fluorouracil (F) 1000 mg/m² per day for 5 days. This regimen was administered every three weeks for 4 cycles in case at least a minor response (≥ 25% reduction in bidimensionally measured tumour size) was observed after 2 cycles. At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines for 7 weeks (PF/RT). Locoregional therapy with radiation was delivered either with a conventional fraction (1.8 Gy - 2.0 Gy once a day, 5 days per week for a total dose of 66 to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week). A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy. Patients on the TPF arm received antibiotic prophylaxis with ciprofloxacin 500 mg orally twice daily for 10 days starting on day 5 of each cycle, or equivalent.

The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, p = 0.0042 (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow up time of 33.7 months. Median overall survival was also significantly longer in favor of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, p = 0.0128. Efficacy results are presented in the table below:

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

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

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

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

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

- Induction chemotherapy followed by chemoradiotherapy (TAX324)

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

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

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

***p-value	0.070	
Best overall response (CR + PR) to study treatment [chemotherapy +/- chemoradiotherapy] (%) (95% CI)	76.5 (70.8-81.5)	71.5 (65.5-77.1)
***p-value	0.209	

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

Pharmacokinetic properties

Absorption

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 - 115 mg/m² in phase I studies. The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the α, β and γ phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Distribution

Following the administration of a 100 mg/m² dose given as a one-hour infusion a mean peak plasma level of 3.7 µg/ml was obtained with a corresponding AUC of 4.6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m² and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

Elimination

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

Special populations

Age and gender

A population pharmacokinetic analysis has been performed with docetaxel in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not altered by the age or sex of the patient.

Hepatic impairment

In a small number of patients (n = 23) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST ≥1.5 times the ULN associated with alkaline phosphatase ≥ 2.5 times the ULN), total clearance was lowered by 27% on average (see Posology and method of administration).

Fluid retention

Docetaxel clearance was not modified in patients with mild to moderate fluid retention and there are no data available in patients with severe fluid retention.

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

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

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

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

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

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

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.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling.

SHELF-LIFE
24 months.

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

After dilution:
From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Once added as recommended into the infusion bag, the docetaxel infusion solution, if stored below 25°C, in non-PVC bags, is stable for 8 hours. It should be used within 8 hours (including the one hour infusion intravenous administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated for 3 days when stored between 2 to 8°C.

SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C.
Store in the original package in order to protect from light. Do not refrigerate or freeze.

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 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.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Docetaxel STADA® is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel STADA® solutions. The use of gloves is recommended.

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

The use of docetaxel should be confined to units specialized 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.

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

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

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

If the vials are stored under refrigeration, allow the required number of boxes of Docetaxel STADA® concentrate for solution for infusion to stand below 25°C for 5 minutes before use.

More than one vial of Docetaxel STADA® concentrate for solution for infusion may be necessary to obtain the required dose for the patient. Aseptically withdraw the required amount of Docetaxel STADA® concentrate for solution for infusion using a calibrated syringe fitted with a 21G needle.

In Docetaxel STADA® 20mg /1 ml vial the concentration of docetaxel is 20 mg/ml.
The required volume of Docetaxel STADA® concentrate for solution for infusion must be injected via a single injection (one shot) into a 250 ml infusion bag or bottle containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for injection.

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

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

The infusion bag solution should be used within 8 hours below 25°C including the one hour infusion to the patient.

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

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

MANUFACTURED BY:
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