(For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only)

TAXTAS 20/80/160
Docetaxel Injection 20 mg/mL - 1 mL, 4 mL & 8 mL Vial

COMPOSITION:
Each ml contains:
Docetaxel Anhydrous Ph. Eur. 20 mg
Dehydrated Alcohol Ph. Eur. 395 mg

DESCRIPTION: A clear pale yellow to brownish yellow solution. When examined under suitable conditions of visibility it should be practically free from foreign particles.

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.

Pharmacodynamics 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 anti-tumour activity against advanced murine and human grafted tumours.

Pharmacokinetic properties:

Absorption:
The pharmacokinetics of Docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m^2 in phase I studies. The kinetic profile of Docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the α, β and γ phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Distribution:
Following the administration of a 100 mg/m^2 dose given as a one-hour infusion a mean peak plasma level of 3.7 µg/ml was obtained with a corresponding AUC of 4.6 h.µg/ml. Mean values

for total body clearance and steady-state volume of distribution were 21 l/h/m^2 and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Docetaxel is more than 95% bound to plasma proteins.

Elimination

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

Special populations

Age and gender

The pharmacokinetics of docetaxel were not altered by the age or sex of the patient.

Hepatic impairment

In a small number of patients (n = 23) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST ≥ 1.5 times the ULN associated with alkaline phosphatase ≥ 2.5 times the ULN), total clearance was lowered by 27% on average (see section 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). The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration.

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.

THERAPEUTIC INDICATIONS:

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

• Docetaxel in combination with doxorubicin is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.
• Docetaxel 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.
• Docetaxel monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer in whom previous therapy has failed. Prior therapy should have included an anthracycline unless clinically contraindicated.
• Non-Small Cell Lung Cancer: Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer even after failure of platinum-based chemotherapy.
• Docetaxel in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition. Docetaxel in combination with carboplatin represents a treatment option to cisplatin-based therapy.
• Squamous Cell Carcinoma of the Head and Neck: Docetaxel is indicated as monotherapy in the treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck after failure of a previous chemotherapy regimen.
• Prostate Cancer: Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostatic cancer.

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

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

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.

POSOLOGY AND METHOD OF ADMINISTRATION:

Recommended dose:

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 Special Warnings and Precautions for use.). Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

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

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 75 mg/m^2 administered 1-hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/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 dose of docetaxel is 100 mg/m^2 in monotherapy. In first-line treatment, docetaxel 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).

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

Non-small cell lung cancer
In chemotherapy, naïve patients treated for non-small cell lung cancer, the recommended dose regimen is docetaxel 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30-60 minutes. For treatment after failure of prior platinum-based chemotherapy, the recommended dose is 75 mg/m^2 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 Pharmacodynamics 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 haematological toxicities. All patients on the docetaxel-containing arm of the TAX 323 and TAX 324 studies, received prophylactic antibiotics.

- Induction chemotherapy followed by radiotherapy (TAX 323)

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

- Induction chemotherapy followed by chemoradiotherapy (TAX 324).

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

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

Squamous Cell Carcinoma of the Head and Neck: The recommended dosage is 100mg/m^2 administered as one hour infusion every three weeks. When use in combination, docetaxel is administered at the recommended dosage of 75mg/m^2."

Dose adjustments during treatment

General

Docetaxel should be administered when the neutrophil count is ≥ 1,500 cells/mm^3.

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

Adjuvant therapy for breast cancer
Studies 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 (e.g., 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 60 mg/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 60 mg/m².

In combination with cisplatin
For patients who are dosed initially at docetaxel 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 25,000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the docetaxel dose in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dose adjustments, see the corresponding summary of product characteristics.

In combination with Capecitabine

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

In combination with cisplatin and 5-fluorouracil
If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. Discontinue treatment if these toxicities persist (see section Special warnings and precautions for use).

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

Toxicity	**Dose 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 SCCHN studies patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g., day 6-15) in all subsequent cycles

Special populations

Patients with hepatic impairment

Based on pharmacokinetic data with docetaxel at 100 mg/m^2 as single agent, patients who have both elevations of transaminase (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 study 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.

Paediatric population

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

Elderly:

Based on a 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).

Route of Administration

Docetaxel Injection is for intravenous routes use only.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to any of the excipients.
Patients with baseline neutrophil count of < 1500 cells/mm^3.
Patients with severe liver impairment.
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 Posology and 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 pretreated 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.

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.

In patients treated with docetaxel in combination with cisplatin and 5fluorouracil (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.

In patients treated with docetaxel in combination with doxorubicin and cyclophosphamide (TAC), febrile neutropenia and/or neutropenic infection occurred at lower rates when patients received primary G-CSF prophylaxis. Primary G-CSF prophylaxis should be considered in patients who receive adjuvant therapy with TAC for breast cancer to mitigate the risk of

complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TAC should be closely monitored.

Hypersensitivity reactions

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

Cutaneous reactions

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

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.

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, study 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

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).

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

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

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 Fertility, pregnancy and lactation).

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

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 Posology and method of administration).

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

Congestive heart failure (CHF)
Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period. In patients treated with the TAC regimen for node positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see sections Undesirable effects and Pharmacodynamics properties).

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

Patients with 4+ nodes
As the benefit observed in patient with 4+ nodes was not statistically significant on disease free survival (DFS) and overall survival (OS), the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis.

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

The incidence of the following adverse events was higher in the elderly patients compared to younger patients. The incidence of the following (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.

Excipients
1 ml vial: This medicinal product contains 50 vol % ethanol anhydrous (alcohol), i.e. up to 395 mg ethanol anhydrous per vial, equivalent to 10 ml of beer or 4 ml wine per vial.

4 ml vial: This medicinal product contains 50 vol % ethanol anhydrous (alcohol), i.e. up to 1.58 g per vial, equivalent to 40 ml of beer or 17 ml wine per vial.

8 ml vial: This medicinal product contains 50 vol % ethanol anhydrous (alcohol), i.e. up to 3.16 g per vial, equivalent to 80 ml of beer or 33 ml wine per vial.

Harmful for those suffering from alcoholism.

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

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

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

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

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, ketoconazole and 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 (e.g., 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.

Docetaxel is highly protein bound (> 95%). Although the possible *in vivo* interaction of docetaxel with concomitantly administered medicinal product 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. Docetaxel did not influence the binding of digitoxin.

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

Fertility, pregnancy and lactation:

Pregnancy
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 child bearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

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

Contraception in males and females
An effective method of contraception should be used during treatment.

Fertility
In non-clinical studies, docetaxel has genotoxic effects and may alter male fertility. 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.

UNDESIRABLE EFFECTS:

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

The following adverse reactions are frequently observed with docetaxel:

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

Nervous system disorders
The development of severe peripheral neurotoxicity requires a reduction of dose. Mild to moderate neurosensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuromotor 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. Severe nail disorders are characterised by hypoor 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.

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

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infections (including sepsis and pneumonia), Infection associated with G4 neutropenia
Blood and lymphatic system disorders	Neutropenia, Anaemia, Febrile neutropenia, Thrombocytopenia
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Peripheral motor neuropathy, Dysgeusia.
Cardiac disorders	Arrhythmia Cardiac failure
Vascular disorders	Hypotension, Hypertension, Haemorrhage.
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Stomatitis Diarrhoea, Nausea Vomiting, Constipation, Abdominal pain, Gastrointestinal haemorrhage,

	Oesophagitis.
Skin and subcutaneous tissue disorders	Alopecia, Skin reaction, Nail disorders
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia
General disorders and administration site conditions	Fluid retention, Asthenia, Pain, Infusion site reaction, Non-cardiac chest pain
Investigations	Blood bilirubin increased, Blood alkaline phosphatase increased, AST increased, ALT increased.

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

Blood and lymphatic system disorders
Rare: bleeding episodes associated with thrombocytopenia.

Tabulated list of adverse reactions in non-small cell lung cancer for Docetaxel 75 mg/m^2 single agent

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infections
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity (no severe)
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Peripheral motor neuropathy.
Cardiac disorders	Arrhythmia (no severe)
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea, Stomatitis, Vomiting, Diarrhoea, Constipation
Skin and subcutaneous tissue disorders	Alopecia, Skin reaction, Nail disorders.
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Asthenia, Fluid retention, Pain.
Investigations	Blood bilirubin increased

Tabulated list of adverse reactions in breast cancer for Docetaxel 75 mg/m^2 in combination with doxorubicin

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infection
Blood and lymphatic system disorders	Neutropenia, Anaemia, Febrile neutropenia, Thrombocytopenia.
Immune system disorders	Hypersensitivity

Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Peripheral motor neuropathy.
Cardiac disorders	Cardiac failure, Arrhythmia (no severe).
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea, Stomatitis, Diarrhoea, Vomiting, Constipation.
Skin and subcutaneous tissue disorders	Alopecia, Nail disorders, Skin reaction (no severe).
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Asthenia Fluid retention, Pain, Infusion site reaction.
Investigations	Blood bilirubin increased, Blood alkaline phosphatase increased, AST increased, ALT increased

Tabulated list of adverse reactions in non-small cell lung cancer for Docetaxel 75 mg/m^2 in combination with cisplatin

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infection
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Peripheral motor neuropathy
Cardiac disorders	Arrhythmia, Cardiac failure.
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea, Vomiting, Diarrhoea, Stomatitis, Constipation.
Skin and subcutaneous tissue disorders	Alopecia, Nail disorders, Skin reaction.
Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Asthenia, Fluid retention, Fever, Infusion site reaction, Pain.
Investigations	Blood bilirubin increased, ALT increased, AST increased, Blood alkaline phosphatase increased.

Tabulated list of adverse reactions in breast cancer for Docetaxel 100 mg/m^2 in combination with trastuzumab

MedDRA system organ classes	**Adverse reactions**

Blood and lymphatic system disorders	Neutropenia, Febrile neutropenia (includes neutropenia associated with fever and antibiotic use), or neutropenic sepsis.
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Insomnia
Nervous system disorders	Paresthesia, Headache, Dysgeusia, Hypoaesthesia.
Eye disorders	Lacrimation increased, Conjunctivitis
Cardiac disorders	Cardiac failure
Vascular disorders	Lymphoedema
Respiratory, thoracic and mediastinal disorders	Epistaxis, Pharyngolaryngeal pain, Nasopharyngitis, Dyspnoea, Cough, Rhinorrhoea.
Gastrointestinal disorders	Nausea, Diarrhoea, Vomiting, Constipation, Stomatitis, Dyspepsia, Abdominal pain.
Skin and subcutaneous tissue disorders	Alopecia, Erythema, Rash, Nail disorders.
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity, Bone pain, Back pain.
General disorders and administration site conditions	Asthenia, Oedema peripheral, Pyrexia, Fatigue, Mucosal inflammation, Pain, Influenza like illness, Chest pain, Chills, Lethargy
Investigations	Weight increased

Tabulated list of adverse reactions in breast cancer for Docetaxel 75 mg/m^2 in combination with capecitabine

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Oral candidiasis
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia.
Metabolism and nutrition disorders	Anorexia, Decreased appetite, Dehydration.
Nervous system disorders	Dysgeusia, Paraesthesia, Dizziness, Headache, Neuropathy peripheral.
Eye disorders	Lacrimation increased
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, Dyspnoea, Cough, Epistaxis.
Gastrointestinal disorders	Stomatitis, Diarrhoea, Nausea, Vomiting, Constipation, Abdominal pain, Dyspepsia, Abdominal pain upper, Dry mouth.
Skin and subcutaneous tissue disorders	Hand-foot syndrome, Alopecia, Nail disorders, Dermatitis, Rash erythematous, Nail discolouration, Onycholysis.
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity, Back pain.
General disorders and	Asthenia, Pyrexia, Fatigue/weakness, Oedema peripheral,

administration site conditions	Lethargy, Pain.
Investigations	Weight decreased, Blood bilirubin increased.

Tabulated list of adverse reactions in prostate cancer for Docetaxel 75 mg/m^2 in combination with prednisone or prednisolone

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infection
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Peripheral sensory neuropathy, Dysgeusia, Peripheral motor neuropathy.
Eye disorders	Lacrimation increased
Cardiac disorders	Cardiac left ventricular function decrease
Respiratory, thoracic and mediastinal disorders	Epistaxis, Dyspnoea, Cough
Gastrointestinal disorders	Nausea, Diarrhoea, Stomatitis/Pharyngitis, Vomiting.
Skin and subcutaneous tissue disorders	Alopecia, Nail disorders (no severe), Exfoliative rash
Musculoskeletal and connective bone disorders	Arthralgia, Myalgia.
General disorders and administration site conditions	Fatigue, Fluid retention.

Tabulated list of adverse reactions in breast cancer for adjuvant therapy with Docetaxel 75 mg/m^2 in combination with doxorubicin and cyclophosphamide in patients with node-positive (TAX 316) and node-negative (GEICAM 9805) breast cancer - pooled data

MedDRA System Organ classes	**Adverse reactions**
Infections and infestations	Infection, Neutropenic infection
Blood and lymphatic system disorders	Anaemia, Neutropenia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Dysgeusia, Peripheral sensory neuropathy, Peripheral motor neuropathy, Syncope, Neurotoxicity, Somnolence.
Eye disorders	Conjunctivitis, Lacrimation increased.
Cardiac disorders	Arrhythmia
Vascular disorders	Hot flush, Hypotension Phlebitis, Lymphoedema
Respiratory, thoracic and mediastinal disorders	Cough.
Gastrointestinal disorders	Nausea, Stomatitis, Vomiting, Diarrhoea, Constipation,

	Abdominal pain
Skin and subcutaneous tissue disorders	Alopecia (persisting), Skin disorder, Nail disorders
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia.
Reproductive system and breast disorders	Amenorrhoea.
General disorders and administration site conditions	Asthenia, Pyrexia, Oedema peripheral.
Investigations	Weight increased Weight decreased

Tabulated list of adverse reactions in gastric adenocarcinoma cancer for Docetaxel 75 mg/m^2 in combination with cisplatin and 5-fluorouracil

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Neutropenic infection, Infection.
Blood and lymphatic system disorders	Anaemia Neutropenia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity.
Metabolism and nutrition disorders	Anorexia.
Nervous system disorders	Peripheral sensory neuropathy, Dizziness, Peripheral motor neuropathy
Eye disorders	Lacrimation increased.
Ear and labyrinth disorders	Hearing impaired.
Cardiac disorders	Arrhythmia
1Gastrointestinal disorders	Diarrhoea, Nausea, Stomatitis, Vomiting, Constipation, Gastrointestinal pain, Oesophagitis / dysphagia / odynophagia
Skin and subcutaneous tissue disorders	Alopecia, Rash pruritus, Nail disorders, Skin exfoliation.
General disorders and administration site conditions	Lethargy, Fever, Fluid retention (severe/life-threatening).

Tabulated list of adverse reactions in head and neck cancer for Docetaxel 75 mg/m^2 in combination with cisplatin and 5-fluorouracil

• Induction chemotherapy followed by radiotherapy (TAX 323)

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infection, Neutropenic infection.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cancer pain.

Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity (no severe).
Metabolism and nutrition disorders	Anorexia.
Nervous system disorders	Dysgeusia / Parosmia, Peripheral sensory neuropathy, Dizziness.
Eye disorders	Lacrimation increased, Conjunctivitis.
Ear and labyrinth disorders	Hearing impaired.
Cardiac disorders	Myocardial ischemia, Arrhythmia.
Vascular disorders	Venous disorder
Gastrointestinal disorders	Nausea, Stomatitis, Diarrhoea, Vomiting, Constipation, Esophagitis/dysphagia/ odynophagia, Abdominal pain, Dyspepsia, Gastrointestinal haemorrhage.
Skin and subcutaneous tissue disorders	Alopecia, Rash pruritic, Dry skin, Skin exfoliative.
Musculoskeletal and connective tissue disorders	Myalgia.
General disorders and administration site conditions	Lethargy, Pyrexia, Fluid retention, Oedema.
Investigations	Weight increased.

• Induction chemotherapy followed by chemoradiotherapy (TAX 324)

MedDRA system organ classes	**Adverse reactions**
Infections and infestations	Infection, Neutropenic infection.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cancer pain.
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia, Febrile neutropenia.
Immune system disorders	Hypersensitivity.
Metabolism and nutrition disorders	Anorexia.
Nervous system disorders	Dysgeusia/Parosmia, Peripheral sensory neuropathy, Dizziness, Peripheral motor neuropathy.
Eye disorders	Lacrimation increased, Conjunctivitis.
Ear and labyrinth disorders	Hearing impaired.
Cardiac disorders	Arrhythmia, Ischemia myocardial.
Vascular disorders	Venous disorder
Gastrointestinal disorders	Nausea, Stomatitis, Vomiting, Diarrhoea, Esophagitis / dysphagia / odynophagia Constipation, Dyspepsia, Gastrointestinal pain, Gastrointestinal haemorrhage.
Skin and subcutaneous tissue	Alopecia, Rash pruritic, Dry skin, Desquamation

disorders	
Musculoskeletal, connective tissue bone disorders	Myalgia.
General disorders and administration site conditions	Lethargy, Pyrexia, Fluid retention, Oedema.
Investigations	Weight decreased.

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.

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:
Unopened vial
2 years

After opening of the vial
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.

Once added to the infusion bag
From a microbiological point of view, dilution must take place in controlled and aseptic conditions and the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Once added as recommended into the infusion bag, the Docetaxel infusion solution, if stored below 25 °C, is stable for 6 hours. It should be used within 6 hours (including the one hour infusion intravenous administration). The infusion solution must not be coupled to the infusion set for more than 8 h at 25 °C.

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 °C to 8 °C.

SPECIAL PRECAUTIONS FOR STORAGE:
Store below 30 °C.
Store in the original package in order to protect from light.
Keep out of the reach and sight of children
For storage conditions of the diluted medicinal product, see section Shelf life.

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

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

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 Injection 20 mg/ml – 1 ml, which contains only 1 vial).

DO NOT use other Docetaxel medicinal products consisting of 2 vials (concentrate and solvent) with this medicinal product (Docetaxel Injection 20 mg/ml – 4 ml, which contains only 1 vial).

DO NOT use other Docetaxel medicinal products consisting of 2 vials (concentrate and solvent) with this medicinal product (Docetaxel Injection 20 mg/ml – 8 ml, which contains only 1 vial).

Docetaxel 20 mg/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 concentrate for solution for infusion to stand below 25 °C for 5 minutes before use. More than one vial of Docetaxel concentrate for solution for infusion may be necessary to obtain the required dose for the patient.

Aseptically withdraw the required amount of Docetaxel concentrate for solution for infusion using a calibrated syringe.

In Taxtas 20 (1 mL vial), the concentration of Docetaxel is 20 mg/mL
In Taxtas 80 (4 mL vial), the concentration of Docetaxel is 20 mg/mL
In Taxtas 160 (8 mL vial), the concentration of Docetaxel is 20 mg/mL

The required volume of Docetaxel concentrate for solution for infusion must be injected via a single injection (one shot) into a 250 ml infusion bag containing either 5% glucose solution or sodium chloride 9 mg/ml (0.9%) solution for infusion.

If a dose greater than 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 manually using a rocking motion.

The infusion bag solution should be used within 6 hours below 25°C including the one hour infusion to the patient.

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

Docetaxel infusion solution is supersaturated and may therefore crystallize over time. If crystals appear, the solution must no longer be used and shall be discarded.

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

MANUFACTURED BY:
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