

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

## Docetaxel Injection Concentrate 20 mg/ml

### DAXOTEL

#### DESCRIPTION:

Docetaxel is a clear, colourless to pale yellow solution. The diluted solution is a clear, colourless solution.

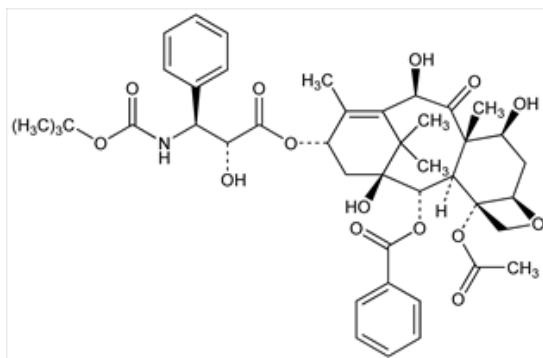
#### COMPOSITION:

Each ml contains:

Docetaxel anhydrous	20 mg
Polysorbate 80 (Purified)	520 mg
Citric Acid Anhydrous	q.s (to adjust pH)
Ethanol Anhydrous	q.s

#### CHEMICAL STRUCTURE:

The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5 $\beta$ -20-epoxy-1,2 $\alpha$ ,4,7 $\beta$ ,10 $\beta$ ,13 $\alpha$ -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate. Docetaxel has the following structural formula:



Docetaxel is a white to off white powder with the empirical formula  $C_{43}H_{53}NO_{14}$  and a molecular weight of 807.9. It is highly lipophilic and practically insoluble in water.

#### PHARMACOLOGY:

##### 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:

Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays. Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some but not all cell lines over expressing the p-glycoprotein which is

encoded by the multidrug resistance gene. *In vivo*, docetaxel is schedule independent and has a broad spectrum of experimental antitumour activity against advanced murine and human grafted tumours.

## **Pharmacokinetics:**

### ***Absorption***

The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the  $\alpha$ ,  $\beta$  and  $\gamma$  phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

### ***Distribution***

Following the administration of a 100 mg/m<sup>2</sup> dose given as a one-hour infusion a mean peak plasma level of 3.7  $\mu$ g/ml was obtained with a corresponding AUC of 4.6 h. $\mu$ g/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m<sup>2</sup> and 113 l, respectively. Inter individual variation in total body clearance was approximately 50 %. Docetaxel is more than 95 % bound to plasma proteins.

### ***Elimination***

Docetaxel is 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.

### ***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***

There is no effect by capecitabine on the pharmacokinetics of docetaxel ( $C_{max}$  and AUC) and no effect by docetaxel on the pharmacokinetics of a relevant capecitabine metabolite 5'-DFUR.

#### ***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 patients with solid tumours had no influence on the pharmacokinetics of each individual medicinal product.

#### ***Prednisone***

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

## **INDICATIONS:**

### Breast cancer

Docetaxel in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with:

- operable node-negative breast cancer.

For patients with operable node-negative breast cancer, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

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

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

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

### Non-small cell lung cancer

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

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

### Prostate cancer

Docetaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer.

### Gastric adenocarcinoma

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

### Ovarian Cancer

Docetaxel is indicated for the treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy.

### 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.

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.

## **CONTRAINDICATIONS:**

Hypersensitivity to the active substance or to any of the excipients.

Patients with baseline neutrophil count of  $< 1,500$  cells/mm<sup>3</sup>.

Patients with severe liver impairment (see sections dosage & administration, precautions & warnings).

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

## **ADVERSE EFFECTS:**

The most commonly reported adverse reactions of docetaxel alone are: neutropenia, 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 neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

### Skin and subcutaneous tissue disorders

Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the arms, face or thorax, and frequently associated with pruritus. Eruptions generally occurred within one week after the docetaxel infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely lead to interruption or discontinuation of docetaxel treatment were reported. 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.

Tabulated list of adverse reactions in breast cancer for docetaxel 100 mg/m<sup>2</sup> single agent

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
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 neuropath), 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	

Tabulated list of adverse reactions in breast cancer for docetaxel 75 mg/m<sup>2</sup> single agent

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>
Infections and infestations	Infections	
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
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<sup>2</sup> in combination with doxorubicin

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
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;	

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
		Arrhythmia	
Vascular disorders			Hypotension
Gastrointestinal disorders	Nausea, Stomatitis, Diarrhoea, Vomiting, 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, Pain	Infusion site reaction	
Investigations		Blood bilirubin increased, Blood alkaline phosphatase increased	AST increased, ALT increased

Tabulated list of adverse reactions in breast cancer for docetaxel 75 mg/m<sup>2</sup> in combination with cisplatin

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
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	Alopecia, Nail		

<b>MedDRA system reactions</b>	<b>Very common Common organ classes adverse adverse</b>	<b>Uncommon adverse reactions</b>
subcutaneous tissue disorders	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 75 mg/m<sup>2</sup> in combination with capecitabine

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>
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 administration site conditions	Asthenia, Pyrexia, Fatigue/weakness, Oedema peripheral	Lethargy; Pain
Investigations		Weight decreased, Blood bilirubin increased

Tabulated list of adverse reactions in breast cancer for docetaxel 75 mg/m<sup>2</sup> in combination with prednisone or prednisolone

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>
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	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<sup>2</sup> in combination with doxorubicin and cyclophosphamide in patients with breast cancer

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
Infections and infestations	Infection, Neutropenic infection		
Blood and lymphatic system disorders	Anaemia, Neutropenia, Thrombocytopenia, Febrile neutropenia		
Immune system disorders		Hypersensitivity	
Metabolism and	Anorexia		

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
nutrition disorders			
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, 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<sup>2</sup> in combination with cisplatin and 5-fluorouracil

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>
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
Gastrointestinal 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	

Tabulated list of adverse reactions in head and neck cancer for docetaxel 75 mg/m<sup>2</sup> in combination with cisplatin and 5-fluorouracil

- Induction chemotherapy followed by radiotherapy

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
Infections and infestations	Infection, Neutropenic infection		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Cancer pain	

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
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	
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

<b>MedDRA system organ classes</b>	<b>Very common adverse reactions</b>	<b>Common adverse reactions</b>	<b>Uncommon adverse reactions</b>
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 disorders	Alopecia, Rash pruritic	Dry skin, Desquamation	
Musculoskeletal, connective tissue bone disorders		Myalgia	
General disorders and administration site conditions	Lethargy, Pyrexia, Fluid retention, Oedema		
Investigations	Weight decreased		Weight increased

## Others

### *Neoplasms benign, malignant and unspecified (including cysts and polyps)*

Cases of second primary malignancies (frequency not known), including non-Hodgkin lymphoma, 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.

Hypersensitivity reactions (frequency not known) have been reported with docetaxel in patients who previously experienced hypersensitivity reactions to paclitaxel.

### *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.

Ventricular arrhythmia including ventricular tachycardia (frequency not known), sometimes fatal, has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/ or cyclophosphamide.

### *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 cases of enterocolitis, including colitis, ischemic colitis, and neutropenic enterocolitis, have been reported with a potential fatal outcome (frequency not known). Rare occurrences of dehydration have been reported as a consequence of gastrointestinal events including enterocolitis and gastrointestinal perforation.

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*

Cases of cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme and severe cutaneous adverse reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported with docetaxel. Scleroderma-like changes usually preceded by peripheral lymphoedema have been reported with docetaxel. Cases of permanent alopecia (frequency not known) 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.

Injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of docetaxel at a different site) has been observed at the site of previous extravasation (frequency not known).

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

#### *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 alcohol in this medicinal product and the side effects of the product may impair the ability to drive or use machines. Therefore, patients should be warned of the potential impact of the amount of alcohol and the side effects of this medicinal product on the ability to drive or use machines and be advised not to drive or use machines if they experience these side effects during treatment.

### **DRUG INTERACTIONS:**

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

Metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and oleandomycin. 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 (see section 4.4). In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49%.

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. In addition, dexamethasone did not affect protein binding of docetaxel. Docetaxel did not influence the binding of digitoxin.

The pharmacokinetics of docetaxel, doxorubicin and cyclophosphamide were not influenced by their co-administration. When combined to docetaxel, the clearance of carboplatin was about 50 % higher than values previously reported for carboplatin monotherapy.

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.

## **PRECAUTIONS AND WARNINGS:**

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.

### Haematology

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

In the case of severe neutropenia (< 500 cells/mm<sup>3</sup> 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 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.

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.

#### Gastrointestinal reactions

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

#### Hypersensitivity reactions

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes 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. Patients who have previously experienced a hypersensitivity reaction to paclitaxel may be at risk to develop hypersensitivity reaction to docetaxel, including more severe hypersensitivity reaction. These patients should be closely monitored during initiation of docetaxel therapy.

#### Cutaneous reactions

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.

Severe Cutaneous Adverse Reactions (SCARs) such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Acute Generalized Exanthematous Pustulosis (AGEP) have been reported with docetaxel treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and closely monitored. If signs and symptoms suggestive of these reactions appear discontinuation of docetaxel should be considered.

#### 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<sup>2</sup> 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<sup>2</sup> 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, the pivotal clinical 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.

Ventricular arrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with docetaxel in combination regimens including doxorubicin, 5-fluorouracil and/ or cyclophosphamide.

Baseline cardiac assessment is recommended.

### 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.

### Second primary malignancies

Second primary malignancies have been reported when docetaxel was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukemia, myelodysplastic syndrome and non-Hodgkin lymphoma) may occur several months or years after docetaxel containing therapy. Patients should be monitored for second primary malignancies.

### Others

Contraceptive measures must be taken by both men and women during treatment and for men at least 6 months after cessation of therapy.

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.

### 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.

#### *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.

#### *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 were 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. Older people treated with TCF should be closely monitored.

### Excipients

This medicinal product contains ethanol (alcohol).

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.

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 patients ability to drive or use machines.

### ***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 potential/Contraception in males and females

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.

### 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.

### 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.

## **DOSAGE AND 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. 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.

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

### Breast cancer

In the adjuvant treatment of operable node-negative breast cancer, the recommended dose of docetaxel is 75 mg/m<sup>2</sup> administered 1-hour after doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> every 3 weeks for 6 cycles (TAC regimen) (see also Dose adjustments during treatment). For the treatment of patients with locally advanced or metastatic breast cancer, the recommended dose of docetaxel is 100 mg/m<sup>2</sup> in monotherapy. In first-line treatment, docetaxel 75 mg/m<sup>2</sup> is given in combination therapy with doxorubicin (50 mg/m<sup>2</sup>).

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

### Non-small cell lung cancer

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

### Prostate cancer

The recommended dose of docetaxel is 75 mg/m<sup>2</sup>. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

### Gastric adenocarcinoma

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

### Ovarian Cancer

The recommended dosage is 100 mg/m<sup>2</sup> administered as one hour infusion every three weeks. When use in combination, docetaxel is administered at the recommended dosage of 75 mg/m<sup>2</sup>.

### Squamous Cell Carcinoma of the Head and Neck

The recommended dosage is 100 mg/m<sup>2</sup> administered as one hour infusion every three weeks. When use in combination, docetaxel is administered at the recommended dosage of 75 mg/m<sup>2</sup>.

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 studies, received prophylactic antibiotics.

- Induction chemotherapy followed by radiotherapy

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<sup>2</sup> as a 1 hour infusion followed by cisplatin 75 mg/m<sup>2</sup> over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m<sup>2</sup> 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

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<sup>2</sup> as a 1 hour intravenous infusion on day 1, followed by cisplatin 100 mg/m<sup>2</sup> administered as a 30-minute to 3-hour infusion, followed by 5-fluorouracil 1000 mg/m<sup>2</sup>/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.

### Dose adjustments during treatment

#### General

Docetaxel should be administered when the neutrophil count is  $\geq 1,500$  cells/mm<sup>3</sup>.

In patients who experienced either febrile neutropenia, neutrophil count  $< 500$  cells/mm<sup>3</sup> 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<sup>2</sup> to 75 mg/m<sup>2</sup> and/or from 75 to 60 mg/m<sup>2</sup>. If the patient continues to experience these reactions at 60 mg/m<sup>2</sup>, the treatment should be discontinued.

#### Adjuvant therapy for breast cancer

Primary G-CSF prophylaxis should be considered in patients who receive docetaxel, doxorubicin and cyclophosphamide (TAC) adjuvant therapy for breast cancer. Patients who experience febrile neutropenia and/or neutropenic infection should have their docetaxel dose reduced to 60 mg/m<sup>2</sup> in all subsequent cycles. Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60 mg/m<sup>2</sup>.

#### In combination with cisplatin

For patients who are dosed initially at docetaxel 75 mg/m<sup>2</sup> in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is  $< 25,000$  cells/mm<sup>3</sup>, 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<sup>2</sup>. 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<sup>2</sup>.
- 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<sup>2</sup>. If subsequent

episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 to 45 mg/m<sup>2</sup>. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 to 60 mg/m<sup>2</sup>. Patients should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level >1,500 cells/mm<sup>3</sup> and platelets recover to a level >100,000 cells/mm<sup>3</sup>. Discontinue treatment if these toxicities persist.

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

<b>Toxicity</b>	<b>Dose adjustment</b>
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.

### Special populations

#### Patients with hepatic impairment

Based on pharmacokinetic data with docetaxel at 100 mg/m<sup>2</sup> 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<sup>2</sup>. 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 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

The safety and efficacy of docetaxel in nasopharyngeal carcinoma in children aged 1 month to less than 18 years have not yet been established.

There is no relevant use of docetaxel in the paediatric population in the indications breast cancer, non-small cell lung cancer, prostate cancer, gastric carcinoma and head and neck cancer, not including type II and III less differentiated nasopharyngeal carcinoma.

### Older people

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

### 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 20 mg/ml concentrate for solution for infusion, 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 for 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 fitted with a 21G needle.

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 or bottle 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 or bottle 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, and solutions containing a precipitate should be discarded.

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

### **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.

**STORAGE:**

Store below 30 °C. Protect from light.

**INCOMPATIBILITIES:**

This medicinal product must not be mixed with other medicinal products except those mentioned in preparation of the infusion solution.

**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.

After dilution

From a microbiological point of view, reconstitution/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.

Chemical and physical in-use stability of the diluted solutions (0.3 mg/ml and 0.74 mg/ml) in the recommended solutions for infusion (5 % glucose solution for infusion or 0.9 % sodium chloride solution for infusion) has been demonstrated for 10 hours at 25°C and for 3 days at 2-8°C when protected from light.

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

**HANDLING AND DISPOSAL:**

Docetaxel is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing the solution. 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.

**DOSAGE FORM AND PACKAGING AVAILABLE:**

Docetaxel Injection Concentrate (DAXOTEL), a single use, sterile, pyrogen-free, non-aqueous solution is supplied as 20 mg/1ml in 6 ml glass vials, 80 mg/4ml in 6 ml glass vials, 120 mg/6ml in 6 ml glass vials, 160 mg/8ml in 10 ml glass vials and 180 mg/9ml in 10 ml glass vials.

Not all pack sizes may be marketed.

**MANUFACTURER INFORMATION:**

**Manufactured in India by:**

**Fresenius Kabi Oncology Ltd.**

Village Kishanpura, Baddi,

Tehsil Nalagarh, Dist. Solan,

Himachal Pradesh IN-174101 INDIA

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