

Data Sheet

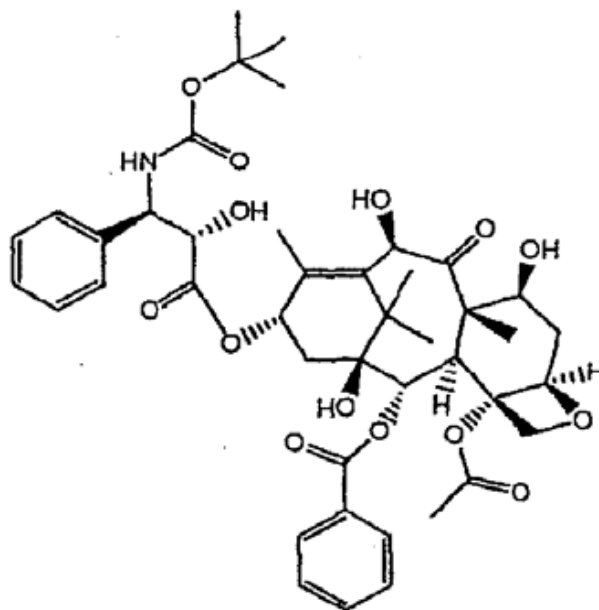
Docetaxel Ebewe

NAME OF THE MEDICINE

Non-proprietary Name

Docetaxel

Chemical Structure



CAS Number

114977-28-5

Chemical name:

(2R, 3S)-N-carboxy-3-phenylisoserine, N-tert-butyl ester, 13 ester with 5 β , 20-epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4- acetate 2- benzoate N-Debenzoyl-N-(tert-butoxycarbonyl)-10-deacetyltaxol.

DESCRIPTION

Docetaxel

Docetaxel is a white to almost white powder with the empirical formula $C_{43}H_{53}NO_{14}$ and a molecular weight of 807.55. It is practically insoluble in water and poorly soluble in hexane, butanol, octanol and propylene glycol.

Docetaxel Ebewe Concentrated Injection

Single-dose vials of Docetaxel Ebewe concentrated injection contains 20 or 80mg of docetaxel (anhydrous). Each mL of docetaxel solution contains 10mg docetaxel anhydrous, 4mg citric acid anhydrous, 648mg macrogol 300, 80mg polysorbate 90, 275.90mg ethanol 96%.

PHARMACOLOGY

Class

Docetaxel Ebewe 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.

Site and Mode of Action

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

Pharmacodynamics

Preclinical Data

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 overexpressing 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. Against transplantable murine tumours *in vivo*, docetaxel was synergistic with vincristine (administered at the same time), etoposide, cyclophosphamide or 5-fluorouracil, but not with vincristine (administered 24 hours apart), cisplatin or doxorubicin.

Pharmacokinetics

Distribution

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 5-115mg/m² in Phase I studies. The kinetic profile of docetaxel is dose-independent and consistent with a three-compartment pharmacokinetic model with half lives for the α , β and γ phases of 4 minutes, 36 minutes and 11.1 hours, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Following the administration of a 100mg/m² dose given as a one-hour infusion a mean peak plasma level of 3.7 μ g/mL was obtained with a corresponding AUC of 4.6h. μ g/mL. Mean values for total body clearance and steady-state volume of distribution were 21 L/h/m² and 113 L, respectively.

Metabolism and Excretion

A study of ¹⁴C-docetaxel has been conducted in three cancer patients. Docetaxel was eliminated in both the urine and faeces following oxidative metabolism of the tert-butyl ester group, within seven days, the urinary and faecal excretion account for about 6% and 75% of the administered

radioactivity, respectively. About 80% of the radioactivity (60% of the administered dose) recovered in faeces is excreted during the first 48 hours as one major and three minor inactive metabolites and very low amounts of unchanged medicine.

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

Docetaxel is more than 95% bound to plasma proteins. Dexamethasone did not affect protein-binding of docetaxel.

The effect of prednisone on the pharmacokinetics of docetaxel administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of docetaxel was observed. Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of docetaxel and the effect of docetaxel on the pharmacokinetics of capecitabine showed no effect of capecitabine on the pharmacokinetics of docetaxel (C_{max} and AUC) and no effect of docetaxel on the pharmacokinetics of the main capecitabine metabolite 5'DFUR.

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

CLINICAL TRIALS

Breast Cancer

Docetaxel as a single agent

Eight Phase II studies were conducted in patients with locally advanced or metastatic breast carcinoma. A total of 172 patients had received no prior chemotherapy (previously untreated) and 111 patients had received prior chemotherapy (previously treated) which included 83 patients who had progressive disease during anthracycline therapy (anthracycline-resistant). In these clinical trials, docetaxel was administered at a 75mg/m² dose in 55 previously untreated patients and 100mg/m² in 117 previously untreated and 111 previously treated patients. In these trials, docetaxel was administered as a one-hour infusion every 3 weeks.

Patients Treated at 75mg/m²

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) was 47% with 9% complete responses (CR). The median duration of response was 34 weeks and the time to progression was 22 weeks.

There was a high response rate in patients with visceral metastases (48.6% in 35 untreated patients).

In patients with ≤ 2 organs involved, the response rate was 58.6% and in patients with ≥ 3 organs involved was 29.4%.

A significant response rate was seen in patients with liver metastases (45% in untreated patients). The same activity is maintained in untreated patients with soft tissue disease (55.5%).

Patients Treated at 100mg/m². Phase II Trials

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) was 56% with 9.4% complete responses (CR). The ORR was 48.6% with 3.6% CR in the previously treated population including 48.2% ORR with 3.6% CR in the anthracycline-resistant patients. The median duration of response was 30 weeks in the previously untreated population, 28 weeks in the previously treated population and 27 weeks in the anthracycline-resistant patients. The time to treatment failure was 21 weeks in the previously untreated population, 19 weeks in the previously treated population and 19 weeks in the anthracycline-resistant patients. The 100mg/m² dose is associated with higher toxicity.

There was a high response rate in patients with visceral metastases (53.8% in 78 untreated patients, 55.1% in 69 pretreated patients and 53.1% in the subgroup of 49 anthracycline-resistant patients).

In patients with ≥ 3 organs involved, the response rate was 54.3% in previously untreated patients, 55.8% in previously treated patients and 50% in the subgroup of anthracycline-resistant patients.

A significant response rate was seen in patients with liver metastases (59.5% in untreated patients, 47.2% in previously treated patients and 40% in the subgroup of anthracycline-resistant patients). The same activity is maintained in patients with visceral involvement (70.4% in previously untreated, 63.6% in previously treated and 63.2% in the subgroup of anthracycline-resistant patients).

Patients Treated at 100mg/m². Phase III Trials

Two randomised Phase III comparative studies, involving a total of 326 alkylating agent-failure and 392 anthracycline-failure metastatic breast cancer patients, have been performed with docetaxel 100mg/m² administered every 3 weeks for seven and ten cycles, respectively.

In alkylating agent-failure patients, there were no significant differences in median time to progression or median survival between docetaxel ("D"; n=161) and doxorubicin ("DX"; n=165; 75mg/m² every 3 weeks) on intent-to-treat and evaluable patient analyses. For the intent-to-treat analysis, median time to progression was 5.9 months for docetaxel and 4.9 months for doxorubicin (D-DX diff: 1.0 months; 95% CI for diff: -0.5 to 1.9); median overall survival was 14.7 months for docetaxel and 14.3 months for doxorubicin (D-DX diff: 0.4 months; 95% CI for diff: -1.9 to 2.7). There was a significant difference in response rates between the two groups: 47.8% for docetaxel and 33.3% for doxorubicin (D-DX diff: 14.5%; 95% CI for diff: 3.9 to 25.0) in intent-to-treat analysis.

In anthracycline-failure patients, docetaxel (n=203) was compared to the combination of mitomycin C and vinblastine ("MV"; n=189; 12mg/m² every 6 weeks and 6mg/m² every 3 weeks, respectively). For the intent-to-treat analysis, docetaxel increased response rate (30% versus 11.6%; D-MV diff: 18.4%; 95% CI for diff: 10.6 to 26.2), prolonged median time to progression (4.3 months versus 2.5 months; D-MV diff: 1.8 months; 95% CI for diff: 1.0 to 2.4) and prolonged median overall survival (11.5 months versus 8.7 months; D-MV diff: 2.8 months; 95% CI for diff: 0.1 to 4.3). Similar results were observed in the evaluable patient analysis.

An open-label, multicentre, randomised Phase III study was conducted to compare docetaxel and paclitaxel in the treatment of advanced breast cancer in patients whose previous therapy should have included an anthracycline. A total of 449 patients were randomised to receive either docetaxel 100mg/m² as a one-hour infusion or paclitaxel 175 mg/m² as a 3-hour infusion. Both regimes were administered every 3 weeks. Efficacy results are described in the following table.

Efficacy of docetaxel versus paclitaxel in the treatment of advanced breast cancer (Intent-to-Treat Analysis, unless specified)

Endpoint	docetaxel 100mg/m ² n=225	paclitaxel 175 mg/m ² n=224	p-value (unadjusted)
Median survival			
(months)	15.3	12.7	0.03
95% CI	(13.3 - 18.5)	(10.5 - 14.8)	
Median time to progression			
(weeks)	24.6	15.6	< 0.01
95% CI	(20 - 30.1)	(13.4 - 18.1)	
*Overall response rate			
(ORR) (%)	32.0	25.0	0.10
95% CI	(25.9 - 38.1)	(19.3 - 30.7)	

*ORR in the evaluable population			
(%)	37.0	26.0	
95% CI	(30.2 - 43.9)	(19.9-31.9)	0.01

*Primary study endpoint

The most frequent adverse events reported for docetaxel were neutropenia, febrile neutropenia, gastrointestinal disorders, neurologic disorders, asthenia and fluid retention. More grade 3/4 events were observed from docetaxel (55.4%) compared to paclitaxel (23.0%). No unexpected toxicities were reported for docetaxel.

Docetaxel in combination with capecitabine

Docetaxel in combination with capecitabine was assessed in an open-label, multicentre, randomised trial. A total of 511 patients with locally advanced and/or metastatic breast cancer resistant to, or recurring after an anthracycline-containing therapy, or relapsing during or recurring within two years of completing an anthracycline-containing adjuvant therapy were enrolled. In this trial, 255 patients were randomised to receive capecitabine (1250mg/m² twice daily for 2 weeks followed by a 1-week rest period) in combination with docetaxel (75mg/m² as a 1-hour intravenous infusion every 3 weeks). 256 patients received docetaxel 100mg/m² alone.

Docetaxel in combination with capecitabine resulted in statistically significant improvements in time to disease progression, overall survival and objective response rate compared to monotherapy with docetaxel as shown in table below. Health-related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ), (C30 version 2, including Breast Cancer Module BR23). HRQoL was similar in the two treatment groups.

Breast cancer combination treatment efficacy results¹

Endpoint Parameter	Capecitabine/ docetaxel N=255	docetaxel N=256	Difference	p-value
Time to Disease Progression				
median	186 days	128 days	HR ² =0.643	
[95% CI]	[165,198]	[105,136]	[0.563, 0.770]	0.0001
Survival				
median	418 days	338 days	HR ² =0.753	0.0119
[95% CI]	[374, 492]	[298, 362]	[0.603, 0.940]	
Response Rate				
	41.6%	29.7%	11.9%	0.0058
[95% CI]	[35.5, 47.9]	[24.2, 35.7]	[3.4, 20.0]	

¹ All-randomised population, Investigator assessment

² Hazard Ratio

Adjuvant Treatment of Breast Cancer

Docetaxel in combination with doxorubicin and cyclophosphamide

Data from a multicentre openlabel randomised trial support the use of docetaxel for the adjuvant treatment of patients with node-positive breast cancer and KPS $\geq 80\%$, between 18 and 70 years of age. After stratification according to the number of positive lymph nodes (1-3, 4+), 1491 patients were randomised to receive either docetaxel $75\text{mg}/\text{m}^2$ administered 1 hour after doxorubicin $50\text{mg}/\text{m}^2$ and cyclophosphamide $500\text{mg}/\text{m}^2$ (DAC arm), or doxorubicin $50\text{mg}/\text{m}^2$ followed by fluorouracil $500\text{mg}/\text{m}^2$ and cyclophosphamide $500\text{mg}/\text{m}^2$ (FAC arm). Both regimens were administered once every 3 weeks for 6 cycles. Docetaxel was administered as a 1- hour infusion, all other medicines were given as IV bolus on day1. G-CSF was administered in both arms as secondary prophylaxis to patients who experienced febrile neutropenia, prolonged neutropenia or neutropenic infection. Patients in the docetaxel arm who continued to experience these reactions remained on G-CSF and had their dose reduced to $60\text{mg}/\text{m}^2$. Patients on the DAC arm received antibiotic prophylaxis with ciprofloxacin 500mg orally b.i.d. for 10 days starting on day 5 of each cycle, or equivalent. In both arms, after the last cycle of chemotherapy, patients with positive oestrogen and/or progesterone receptors received tamoxifen 20mg daily for up to 5 years. Adjuvant radiation therapy was prescribed according to guidelines in place at participating institutions and was given to 69% of patients who received DAC and 72% of patients who received FAC.

An interim analysis was performed with a median follow-up of 55 months. Significantly longer disease-free survival for the DAC arm compared to the FAC arm was demonstrated. In the DAC arm, 23% of subjects had experienced disease progression, compared to 30% in the FAC arm. DAC-treated patients had a 28% reduction in the risk of relapse compared to those treated with FAC (hazard ratio=0.72, 95% CI (0.59-0.88), $p=0.001$). Overall survival was also significantly longer in the DAC arm with DAC-treated patients having a 30% reduction in the risk of death compared to FAC (hazard ratio=0.70, 95% CI (0.53-0.91), $p=0.008$). In the DAC arm, 12% of patients had died compared to 17% on the FAC arm.

In the adjuvant breast cancer trial (TAX316), docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients. DAC-treated patient subsets according to prospectively defined major prognostic factors were analysed:

Analysis of DAC-treated patient subsets

Patient subset	Number of patients	Disease Free Survival			Overall Survival		
		Hazard ratio*	95% CI	P=	Hazard ratio*	95% CI	P=
No of positive nodes							
Overall	745	0.72	0.59-0.88	0.001	0.70	0.53-0.91	0.008
1-3	467	0.61	0.46-0.82	0.0009	0.45	0.29-0.70	0.0002
4+	278	0.83	0.63-1.08	0.17	0.94	0.66-1.33	0.72
Hormone Receptor status							
Positive	567	0.72	0.56-0.92	0.0076	0.69	0.48-1.00	0.0459
Negative	178	0.69	0.49-0.97	0.0296	0.66	0.44-0.98	0.0389
Her-2 neu status							
Positive	155	0.60	0.41-0.88	0.0088	0.74	0.45-1.20	0.22
Negative	475	0.76	0.59-1.00	0.046	0.63	0.44-0.91	0.0135

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

The beneficial effect of DAC was seen in both hormone receptor positive and negative patients.

Combination with Doxorubicin, Cyclophosphamide and Trastuzumab and with Carboplatin and Trastuzumab (HER2+)

The efficacy and safety of docetaxel in combination with trastuzumab was studied for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2 (with node positive and high risk node negative). A total of 3,222 women were randomised in the study, and 3,174 were treated with either: AC-T, AC-TH, or TCH.

- **AC-T** (control arm): Doxorubicin 60 mg/m² IV in combination with cyclophosphamide 600 mg/m² IV every 3 weeks for 4 cycles, followed by docetaxel 100 mg/m² as a 1-hour IV infusion every 3 weeks for 4 cycles;

- **AC-TH**: Doxorubicin 60 mg/m² IV in combination with cyclophosphamide 600 mg/m² IV every 3 weeks for 4 cycles. Three weeks after the last cycle of AC, trastuzumab 4 mg/kg loading dose by IV infusion over 90 minutes on day 1 of cycle 5 was administered, followed by trastuzumab 2 mg/kg by IV infusion over 30-minutes weekly starting day 8 of cycle 5; and docetaxel 100 mg/m² administered by IV infusion over 1-hour on day 2 of cycle 5, then on day 1 every 3 weeks for a total of 4 cycles of docetaxel. Beginning three weeks after

the last cycle of chemotherapy, trastuzumab 6 mg/kg by IV infusion over 30 minutes was given every 3 weeks (for 1 year from the date of first administration);

- **TCH:** Trastuzumab 4 mg/kg loading dose by IV infusion over 90 minutes on day 1 of cycle 1 only, followed by trastuzumab 2 mg/kg by IV infusion over 30 minutes weekly starting on day 8 until three weeks after the last cycle of chemotherapy. Docetaxel 75 mg/m² was administered on day 2 of cycle 1, then on day 1 of all subsequent cycles by IV infusion over 1 hour followed by carboplatin (AUC 6 mg/mL/min) as a 30-60 minute IV infusion, for a total of six cycles of docetaxel and carboplatin. Beginning three weeks after the last cycle of chemotherapy, trastuzumab 6 mg/kg by IV infusion over 30 minutes was given every 3 weeks (for 1 year from the date of first administration).

The patients and disease characteristics at baseline were well balanced between the 3 treatment arms.

Disease Free Survival (DFS) was the primary endpoint, and Overall Survival (OS) was the secondary endpoint.

Results of the second interim analysis, performed with a median follow-up of 36 months, demonstrated that docetaxel and trastuzumab given concurrently as part of either an anthracycline-based (AC-TH) or non-anthracycline-based (TCH) adjuvant treatment regimens, for patients with HER2-positive operable breast cancer, statistically prolonged both DFS and OS compared with the control arm (AC-T). The relative reduction in the risk of relapse was 39 % (p < 0.0001) and 33% (p = 0.0003) for the AC-TH and TCH arms, respectively, compared with the AC-T arm. The relative reduction in the risk of death was 42% (p = 0.0024) and 34% (p = 0.0182) for the AC-TH and TCH arms, respectively, compared with the AC-T arm. There was no statistically significant difference between the two trastuzumab-containing arms AC-TH and TCH for DFS and OS. Efficacy results are summarised in the following table:

Doxorubicin and cyclophosphamide followed by docetaxel in combination with trastuzumab, or docetaxel in combination with trastuzumab, and carboplatin (Intent-to-Treat Population)

	Disease Free Survival (DFS)			Overall Survival (OS)		
	AC-T n=1073	AC-TH n=1074	TCH n=1075	AC-T n=1073	AC-TH n=1074	TCH n=1075
Stratified analysis						
Hazard ratio ^a	NA	0.61	0.67	NA	0.58	0.66
95% CI	NA	(0.49-0.77)	(0.54-0.83)	NA	(0.40-0.83)	(0.47-0.93)
p-value ^b	NA	< 0.0001	0.0003	NA	0.0024	0.0182
Percent	80.9%	86.7%	85.5%	93.0%	95.5%	95.2%

event-free at 3 years (95% CI)	(78.3-83.5%)	(84.4-89.0%)	(83.2-87.9%)	(91.2-94.8%)	(94.0-96.9%)	(93.7-96.6%)
Absolute benefit ^c		5.8% (2.3-9.2%)	4.6% (1.2-8.1%)		2.5% (0.2-4.8%)	2.2% (-0.1-4.5%)

AC-T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC-TH=doxorubicin plus cyclophosphamide, followed by docetaxel in combination with trastuzumab; TCH=docetaxel in combination with trastuzumab and carboplatin.

CI=confidence interval; NA=not applicable.

^a=Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status.

^b=Stratified log-rank p-value.

^c=Absolute benefit in percent event-free compared to AC-T at 3 years.

There were 29% of patients with high risk node-negative disease included in the study. The benefit observed for the overall population was irrespective of the nodal status.

Disease Free Survival (Intent-to-Treat Population) according to Nodal Status:

	High risk node-negative patients			Node-positive patients		
	AC-T n = 309	AC-TH n = 306	TCH n = 307	AC-T n = 764	AC-TH n = 768	TCH n = 768
Stratified analysis						
Hazard ratio ^a	NA	0.36	0.52	NA	0.67	0.70
95% CI	NA	(0.19-0.68)	(0.30-0.92)	NA	(0.53-0.85)	(0.56-0.89)
p-value ^b	NA	0.0010	0.0209	NA	0.0008	0.0029
Percent event-free at 3 years (95% CI)	88.0% (84.1-91.9%)	94.8% (91.9-97.8%)	93.0% (89.9-96.2%)	78.1% (74.9-81.3%)	83.6% (80.7-86.5%)	82.6% (79.6-85.6%)
Absolute benefit ^c		6.8% (1.9-11.7%)	5.1% (0.0-10.1%)		5.5% (1.2-9.8%)	4.6% (0.2-8.9%)

AC-T=doxorubicin plus cyclophosphamide, followed by docetaxel; AC-TH=doxorubicin plus cyclophosphamide, followed by docetaxel in combination with trastuzumab; TCH=docetaxel in combination with trastuzumab and carboplatin.

CI=confidence interval; NA=not applicable.

^a=Relative to AC-T. Estimated using Cox regression stratified by number of nodes and hormonal receptor status.

^b=Stratified log-rank p-value.

^c=Absolute benefit in percent event free compared with AC-T.

Non-Small Cell Lung Cancer

Patients Treated at 75mg/m²

One phase II study was conducted in 20 previously untreated patients with locally advanced or metastatic non-small cell lung cancer. In this clinical trial, docetaxel was administered at a 75mg/m² dose given as a one-hour infusion every 3 weeks. The response rate was 10%.

Patients Treated at 100mg/m²

Six phase II studies were conducted in patients with locally advanced or metastatic non small cell lung cancer. A total of 160 patients had received no prior chemotherapy (previously untreated) and 88 patients had received prior platinum-based chemotherapy (previously treated) which included 37 patients who had progressive disease with platinum therapy (platinum refractory). In these clinical trials, docetaxel was administered at a 100mg/m² dose given as a one-hour infusion every 3 weeks.

The 100mg/m² dose is associated with higher toxicity.

In the intent-to-treat analysis on previously untreated patients, the overall response rate (ORR) was 26.9% and in the previously treated population it was 17%.

The survival time for all previously untreated patients or previously treated patients was 9 and 8 months, respectively.

Prostate Cancer

The safety and efficacy of docetaxel in patients with androgen-independent (hormone refractory) metastatic prostate cancer were evaluated in a randomised multicentre Phase III trial. A total of 1006 patients with KPS ≥60 were randomised to the following treatment groups:

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

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

Patients who received docetaxel every three weeks demonstrated significantly longer overall survival compared to those treated with mitozantrone (p=0.0094). The increase in survival seen in the docetaxel weekly arm was not statistically significant compared to the mitozantrone control arm. Efficacy endpoints for the docetaxel 3-weekly arm versus the control arm are summarised in the following table:

Efficacy of docetaxel in the treatment of patients with androgen-independent (hormone refractory) prostate cancer (intent-to-treat analysis)

Endpoint	Docetaxel Every 3 weeks	Mitozantrone Every 3 weeks
Number of patients	335	337
Median survival (months)	18.9	16.5
95% CI	(17.0-21.2)	(14.4-18.6)
Hazard ratio	0.761	-
95% CI	(0.619-0.936)	-
p value ⁺ *	0.0094	-
Number of patients	291	300
PSA** response rate (%)	45.4	31.7
95% CI	(39.5-51.3)	(26.4-37.3)
p-value*	0.0005	-
Number of patients	153	157
Pain response rate (%)	34.6	21.7
95% CI	(27.1-42.7)	(15.5-28.9)
p-value*	0.0107	-
Number of patients	141	137
Tumour response rate (%)	12.1	6.6
95% CI	(7.2-18.6)	(3.0-12.1)
p-value*	0.1112	-

⁺ stratified log rank test

* threshold for statistical significance=0.0175

** PSA: Prostate-Specific Antigen

Head and Neck Cancer

Induction chemotherapy followed by radiotherapy (TAX323)

The safety and efficacy of docetaxel in the induction treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a phase III, multicentre, open-label, randomised trial (TAX 323). In this study, 358 previously untreated patients with locally advanced inoperable stage III/IV SCCHN, and WHO performance status 0 or 1, were randomised to one of two treatment arms. Patients on the docetaxel arm received docetaxel (T) 75mg/m² followed by cisplatin (P) 75mg/m² on Day 1, followed by fluorouracil (F) 750mg/m² per day as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Premedication for docetaxel included corticosteroids and antibiotics. Patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines (TPF/RT). Patients on the comparator arm received cisplatin 100mg/m² on Day 1, followed by fluorouracil 1000mg/m² (PF) as a continuous infusion on Days 1-5. The cycles were repeated every three weeks for 4 cycles. Patients whose disease did not progress received RT according to institutional

guidelines (PF/RT). At the end of chemotherapy, with a minimal interval of 4 weeks and a maximal interval of 7 weeks, patients whose disease did not progress received radiotherapy (RT) according to institutional guidelines.

Conventional locoregional radiotherapy was given to approximately 77% of the patients at a total dose of 66 - 70 Gy (1.8 Gy - 2.0 Gy once a day, 5 days per week) while accelerated/hyperfractionated regimens of radiation therapy were used in approximately 23% of patients (twice a day, with a minimum interfraction interval of 6 hours, 5 days per week).

A total of 70 Gy was recommended for accelerated regimens and 74 Gy for hyperfractionated schemes. Surgical resection was allowed following chemotherapy, before or after radiotherapy. The primary endpoint in this study, progression-free survival (PFS), was significantly longer in the TPF arm compared to the PF arm, $p=0.0042$ (median PFS: 11.4 vs. 8.3 months respectively) with an overall median follow-up time of 33.7 months. Median overall survival was significantly longer in favour of the TPF arm compared to the PF arm (median OS: 18.6 vs. 14.5 months respectively) with a 28% risk reduction of mortality, $p=0.0128$. Patients with tumours of the nasopharynx and the nasal/paranasal cavities were excluded from this study. Efficacy results are presented in the table below.

Efficacy of docetaxel in the induction treatment of patients with locally advanced inoperable SCCHN (intent-to-treat analysis)

Endpoint	docetaxel + Cis + FU n=177	Cis + FU n=181
Median progression free survival (months)	11.4	8.3
(95% CI)	(10.1 - 14.0)	(7.4 - 9.1)
Adjusted Hazard Ratio	0.70	
(95% CI)	(0.55 - 0.89)	
*p-value	0.0042	
Median survival (months)	18.6	14.5
(95% CI)	(15.7 - 24.0)	(11.6 - 18.7)
Hazard Ratio	0.72	
(95% CI)	(0.56 - 0.93)	
**p-value	0.0128	
Overall response rate to chemotherapy (%)	67.8	53.6
(95% CI)	(60.4 - 74.6)	(46.0 - 61.0)
***p-value	0.006	

Overall response rate to study treatment [chemo- ± radio-therapy (%)]	72.3	58.6
(95% CI)	(65.1 - 78.8)	(51.0 - 65.8)
***p-value	0.006	
Median duration of response to chemo- ± radio-therapy	n=128	n=106
(months)	15.7	11.7
(95% CI)	(13.4 - 24.6)	(10.2 - 17.4)
Hazard Ratio	0.72	
(95% CI)	(0.52 - 0.99)	
**p-value	0.0457	

A Hazard Ratio of less than 1 favours docetaxel + Cisplatin + FU

* Cox model (adjustment for Primary tumour site, T and N clinical stages and PSWHO)

** Logrank test

*** Chi-square test

Clinical Benefit Parameters

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

The performance status scale for head and neck, designed to measure disturbances of speech and eating, was significantly in favour of TPF treatment.

The median time to first deterioration of WHO performance status was significantly (p=0.0158) longer in the TPF arm (13.7 months; 95% CI: 10.7 - 21.0 months) compared to PF (8.3 months; 95% CI: 7.3 - 9.6 months).

However, no significant difference in WHO performance status was apparent between the two arms (odds ratio = 0.96, 95% CI: 0.66 - 1.41). There was no difference in pain intensity in patients treated with TPF or PF.

Induction chemotherapy followed by chemoradiotherapy (TAX324)

The safety and efficacy of docetaxel in the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN was evaluated in a randomised, multicentre open-label, phase III trial (TAX324). In this study, 501 patients with locally advanced SCCHN, and a WHO performance status of 0 or 1 were randomised to one of two arms.

Patients on the docetaxel arm received docetaxel (T) 75 mg/m² by IV infusion on day 1, followed by cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 4. The cycles were repeated every 3

weeks for 3 cycles. Premedication for docetaxel included corticosteroids and antibiotics. All patients who did not have progressive disease were to receive chemoradiotherapy (CRT) as per protocol (TPF/CRT). Patients on the comparator arm received cisplatin (P) 100 mg/m² administered as a 30-minute to three-hour IV infusion, followed by the continuous IV infusion of fluorouracil (F) 1000 mg/m²/day from day 1 to day 5. The cycles were repeated every 3 weeks for 3 cycles. All patients who did not have progressive disease were to receive CRT as per protocol (PF/CRT).

Patients in both treatment arms were to receive 7 weeks of CRT following induction chemotherapy with a minimum interval of 3 weeks and no later than 8 weeks after start of the last cycle (day 22 to day 56 of last cycle). During radiotherapy, carboplatin (AUC 1.5) was given weekly as a one-hour IV infusion for a maximum of 7 doses. Radiation was delivered with megavoltage equipment using once daily fractionation (2 Gy per day, 5 days per week for 7 weeks, for a total dose of 70 - 72 Gy). Surgery on the primary site of disease and/or neck could be considered at any time following completion of CRT.

The primary efficacy endpoint in this study, overall survival (OS) was significantly longer (log-rank test p=0.0058) with the docetaxel-containing regimen compared to PF (median OS: 70.6 vs 30.1 months respectively), with a 30% risk reduction in mortality compared to PF (hazard ratio (HR)= 0.70, 95% confidence interval (CI)= 0.54 - 0.90). The secondary endpoint PFS demonstrated a 29% risk reduction of progression or death and a 22-month improvement in median PFS (35.5 months for TPF and 13.1 for PF). This was also statistically significant with an HR of 0.71; 95% CI 0.56 - 0.90; log-rank test p=0.004. Efficacy results are presented in the table below.

Efficacy of docetaxel in the induction treatment followed by chemoradiotherapy for patients with locally advanced SCCHN (Intent-to-treat analysis)

Endpoint	docetaxel + Cis + FU n=255	Cis + FU n=246
Median overall survival (months)	70.6	30.1
(95% CI)	(49.0 - N/A)	(20.9 - 51.5)
Hazard Ratio	0.70	
(95% CI)	(0.54 - 0.90)	
*p-value	0.0058	
Median progression free survival (months)	35.5	13.1
(95% CI)	(19.3 - N/A)	(10.6 - 20.2)
Hazard Ratio	0.71	
(95% CI)	(0.56 - 0.90)	
**p-value	0.004	
Best overall response (CR + PR) to chemotherapy (%)	71.8	64.2

(95% CI)	(65.8 - 77.2)	(57.9 - 70.2)
***p-value	0.070	
Best overall response (CR + PR) to study treatment [chemotherapy ± chemoradiotherapy] (%)	76.5	71.5
(95% CI)	(70.8 - 81.5)	(65.5 - 77.1)
***p-value	0.209	

A Hazard Ratio of less than 1 favours docetaxel + Cisplatin + FU

* unadjusted log-rank test

** unadjusted log-rank test, not adjusted for multiple comparisons

*** Chi-square test, not adjusted for multiple comparisons

N/A - not applicable

INDICATIONS

Breast Cancer

Metastatic Breast Cancer

Docetaxel Ebewe is indicated for the treatment of patients with locally advanced or metastatic breast cancer in whom previous chemotherapy has failed.

Docetaxel Ebewe in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

Adjuvant Treatment of Breast Cancer

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

Doxorubicin and cyclophosphamide followed by Docetaxel Ebewe in combination with trastuzumab (AC-TH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

Docetaxel Ebewe in combination with carboplatin and trastuzumab (TCH) is indicated for the adjuvant treatment of patients with operable breast cancer whose tumours overexpress HER2.

Non-Small Cell Lung Cancer

Docetaxel is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, including those who have failed platinum-based chemotherapy.

Prostate Cancer

Docetaxel Ebewe is indicated for the treatment of patients with androgen independent (hormone refractory) prostate cancer.

Head and Neck Cancer

Docetaxel Ebewe in combination with cisplatin and fluorouracil is indicated in the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

CONTRAINDICATIONS

Docetaxel Ebewe is contraindicated in patients who have a history of severe hypersensitivity reactions to Docetaxel Ebewe or any other ingredients listed at the start of this Datasheet.

Docetaxel Ebewe should not be used in patients with baseline neutrophil count of $<1.5 \text{ cells} \times 10^9/\text{L}$.

Docetaxel Ebewe should not be used in patients with severe liver impairment.

Docetaxel Ebewe should not be used in pregnant or breast-feeding women.

Contraindications that apply for other medicines also apply when these medicines are combined with Docetaxel Ebewe.

PRECAUTIONS

The use of Docetaxel Ebewe should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist.

Premedication

Patients should be pre-treated prior to each Docetaxel Ebewe administration. A premedication consisting of an oral corticosteroid such as dexamethasone 16mg per day (e.g. 8mg twice daily) for 3 days starting one day prior to Docetaxel Ebewe administration can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. (see **Fluid Retention** and **Hypersensitivity Reaction** sections below, and refer to **DOSAGE AND ADMINISTRATION**)

For prostate cancer, the premedication is oral dexamethasone 8mg, 12 hours, 3 hours and 1 hour before the docetaxel infusion.

Haematology

Bone marrow suppression and other haematologic effects to docetaxel include neutropenia, the most frequent adverse effect of docetaxel (see **ADVERSE EFFECTS, Clinical Studies**).

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 in all patients receiving docetaxel. Patients should be retreated with docetaxel only when neutrophils recover to a level ≥ 1.5 cells $\times 10^9/L$.

Docetaxel Ebewe should not be administered to patients with baseline neutrophil counts of less than < 1.5 cells $\times 10^9/L$. Frequent monitoring of complete blood counts should be conducted on all patients during treatment with docetaxel. Patients should not be retreated with Docetaxel Ebewe until neutrophils recover to a level ≥ 1.5 cells $\times 10^9/L$. (see **DOSAGE AND ADMINISTRATION**).

In the case of severe neutropenia (< 0.5 cells $\times 10^9/L$ for seven days or more) during a course of Docetaxel Ebewe therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended. Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel Ebewe dose reduced (see also **Dosage Adjustments During Treatment**).

In the treatment of adjuvant breast cancer, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow-up (see **ADVERSE EFFECTS**).

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes, during or immediately following the cessation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. Frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and medicine fever or chills. 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 aggressive therapy.

Severe symptoms are usually resolved after discontinuing the infusion and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with docetaxel.

Cutaneous Reactions

Reversible cutaneous reactions were generally mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on feet, hands (including severe hand and foot syndrome), but also 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 led to interruption or discontinuation of docetaxel treatment were reported. Nail disorders were characterised by hypo- or hyperpigmentation, pain and onycholysis.

Very rare cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes have been reported with docetaxel. In some cases multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects.

Ear and Labyrinth Disorders

Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic medicines.

Fluid Retention

A premedication consisting of an oral corticosteroid such as dexamethasone 16mg per day (e.g. 8mg twice daily) for 3 days starting one day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION**).

The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kgs or more. Fluid retention is cumulative in incidence and severity; however, it has been reported in some patients during early courses of therapy. The median cumulative dose to onset for treatment with 75mg/m² is 524mg/m² and treatment at 100mg/m² is 509mg/m² (without premedication) and 797mg/m² (with premedication). Fluid retention is slowly reversible after docetaxel treatment is stopped. In patients treated by docetaxel as single agent, at 100mg/m², the median cumulative dose to treatment discontinuation was more than 1,000 mg/m² and the median time to fluid retention reversibility was 16.4 weeks (range 0 to 42 weeks). Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

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

Patients with Liver Impairment

Liver function tests (LFTs) should be measured at baseline and before each cycle.

In patients treated with docetaxel at 100mg/m² who have both elevations of serum transaminase values (ALT and/or AST) greater than 1.5 times the upper limit of normal (ULN) and increases in alkaline phosphatase greater than 2.5 times the ULN, there is a greater risk of developing severe adverse effects such as toxic deaths including sepsis, gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. The recommended dose of docetaxel in patients with elevated LFTs is 75mg/m² (see **DOSAGE AND ADMINISTRATION**).

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

Nervous System

The development of severe neurosensory signs and/or symptoms have been observed in patients and requires a reduction of dose (see **DOSAGE AND ADMINISTRATION**).

Cardiac Toxicity

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

Carcinogenicity

Docetaxel was not mutagenic in bacterial or CHO/HPRT gene mutation assays, but was mutagenic in the *in vitro* chromosome aberration assay, in the *in vivo* micronucleus test in the mouse and modified the distribution of CHO-K1 cells in the cell cycle phases.

The carcinogenic potential of docetaxel has not been studied. However, based upon its pharmacodynamic mechanism of action, docetaxel may be a carcinogen.

Studies in mice have shown that IV doses of 144mg/m² or 30mg/m²/day for 5 days are associated with testicular atrophy, mineralisation and degeneration of tubular germinal epithelium, Leydig cell hyperplasia, epididymal hypospermia, and follicular atresia in the ovaries. Studies in rats have shown that intravenous doses of 120mg/m² are associated with testicular atrophy, germ cell atrophy, Leydig cell hyperplasia and mineralisation. The rodent studies suggest that docetaxel may impair fertility. Studies in rats have also shown that IV doses of 0.9mg/m²/day to both sexes are associated with reduced litter averages for corpora lutea, implantations and live foetuses, and increased litter averages for early and total resorptions. Larger doses to both sexes (males 1.8mg/m²/day, females 1.35mg/m²/day) are additionally associated with increased time to mating, increased number of dams with total resorption, and reduced male foetal body weight.

Use in Pregnancy

Category D: medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations of irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Docetaxel may cause foetal harm when administered to a pregnant woman. Foetal radioactivity has been detected following intravenous (IV) administration of radiolabelled docetaxel to pregnant rats. Docetaxel has been shown to be embryo- and foetotoxic in rats and rabbits. At IV doses of 0.9mg/m², docetaxel caused fewer corpora lutea, fewer implantations, increased resorptions and embryofoetal deaths in rats. No evidence of teratogenic effects was found when docetaxel was administered IV at doses up to 1.8mg/m² or 1.2mg/m² in rats or rabbits, respectively, but reduced foetal weight and delayed ossification were observed.

Offspring from rats receiving docetaxel 1.5mg/m²/day IV from late gestation until weaning showed signs of delayed development. No studies have been performed in pregnant women.

If docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, she should be appraised of the potential hazard.

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with this medicine. Contraceptive measures must be taken during and for at least three months after cessation of therapy with docetaxel.

Use in Lactation

Radioactivity has been detected in milk following intravenous administration of radiolabelled docetaxel to lactating rats. Offspring from rats receiving docetaxel 1.5mg/m²/day IV during late gestation and lactation showed signs of delayed development. It is not known whether docetaxel is excreted in human milk. It is recommended to advise women not to breast-feed during treatment with docetaxel.

Paediatric Use

The safety and effectiveness of Docetaxel Ebewe in children have not been established.

Use in the Elderly

An analysis of safety data in patients equal to or greater than 60 years of age treated with docetaxel in combination with capecitabine showed an increase in the incidence of treatment-related Grade 3 or 4 adverse effects, treatment-related serious adverse effects and early withdrawals from treatment due to adverse effects compared to patients less than 60 years of age.

Of the 333 patients treated with docetaxel every three weeks in the prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. Differences in efficacy were not identified between elderly patients and younger patients. In patients treated with docetaxel every three weeks, the incidence of anaemia, infection, nail changes, anorexia, weight loss occurred at rates $\geq 10\%$ higher in patients who were 65 years of age or greater compared to younger patients.

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

Of the 174 and 251 patients who received the induction treatment with docetaxel in combination with cisplatin and fluorouracil (TPF) for SCCHN in the TAX323 and TAX324 studies, only 18 (10%) and 32 (13%), respectively, of the patients were 65 years of age or older. The number of elderly patients who received this regimen was not sufficient to determine whether geriatric patients responded differently from younger patients.

The proportion of elderly patients was 5.5% and 6.6% in the AC-TH and TCH regimens, respectively, and is too limited to allow for conclusions regarding the adverse events occurring by age (< 65 years vs ≥ 65 years).

Recommendations for Safe Handling

Docetaxel Ebewe is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing Docetaxel Ebewe solutions. The use of gloves is recommended.

If Docetaxel Ebewe concentrate or infusion solution comes into contact with the skin, wash immediately and thoroughly with soap and water.

If Docetaxel Ebewe concentrate or infusion solution comes into contact with mucous membranes, wash immediately and thoroughly with water.

INTERACTIONS WITH OTHER MEDICINES

There have been no formal clinical studies to evaluate the medicine interactions of docetaxel.

In vitro studies suggest that isoenzymes of the cytochrome P450-3A subfamily appear to be involved in the hepatic metabolism of docetaxel in humans. *In vitro*, the biotransformation of docetaxel was inhibited by cyclosporin, terfenadine, ketoconazole, erythromycin and troleandomycin and to a lesser extent by doxorubicin, vinorelbine, vinblastine and nifedipine, increased by dexamethasone, phenobarbitone and clofibrate and unaffected by cimetidine, ranitidine, omeprazole, diazepam, imipramine, paracetamol, caffeine, tolbutamide and quinidine. Strong P450-3A inhibitors may affect

docetaxel metabolism *in vivo*, necessitating caution in co-administration regimens.

In vitro, plasma protein binding was more than 95%, with the important proteins being albumin, α 1-acid glycoprotein and lipoproteins. The *in vitro* plasma protein binding of docetaxel was not affected by dexamethasone, erythromycin, salicylate, sulfamethoxazole, diphenhydramine, propranolol, propafenone, phenytoin and sodium valproate. The binding of digitoxin was not affected by docetaxel.

In vivo investigations show that caution should be exercised when administering ketoconazole to patients as concomitant therapy since there is a potential for a significant interaction.

Docetaxel should be administered with caution in patients concomitantly receiving protease inhibitors (e.g., ritonavir) which are inhibitors and substrates of cytochrome P450-3A.

ADVERSE EFFECTS

Clinical Studies

Monotherapy

Breast and Non-Small Cell Lung Cancer

The adverse effects considered to be possibly or probably related to starting the administration of docetaxel have been obtained from 75 patients who received a dose of 75mg/m² without the recommended premedication, and from 2106 (2045 with normal* and 61 with elevated* LFTs at baseline) patients who received an initially planned dose of 100mg/m² over a one-hour infusion every 3 weeks independently of the pre-medication. The patients were enrolled in 40 phase II and III studies conducted in Europe and North America (991 with breast carcinoma, 668 with non-small cell lung carcinoma and 447 with various tumour types).

The safety profile is generally similar between patients receiving docetaxel for the treatment of breast, non small cell lung or ovarian carcinoma.

The following table lists the adverse effect data:

Summary of adverse events in patients receiving docetaxel at 75 and 100mg/m² as a single agent

	Normal LFTs* at Baseline		Elevated LFTs* at Baseline
Docetaxel dosage	75 mg/m ²	100 mg/m ²	100 mg/m ²
Number of patients	n=75 %	n=2045 %	n=61 %

Haematological Toxicity			
<i>Neutropenia</i>			
ANC ⁻ <2.0 cells x 10 ⁹ /L	-	95.5	96.4
ANC ⁻ <0.5 cells x 10 ⁹ /L	73.0	75.4	87.5
<i>Febrile neutropenia</i>			
<i>(fever/ANC⁻ <0.5 x 10⁹/L):</i>			
by patient	-	11.0	26.2
by cycle	-	2.6*	8.7
<i>(fever/ANC⁻ <1 x 10⁹/L):</i>			
by patient	5.0	-	-
by cycle	1.5	-	-
<i>Thrombocytopenia</i>			
<100 cells x 10 ⁹ /L	6.7	8.0	24.6
<i>Anaemia</i>			
<110 g/L	86.7	90.4	91.8
<80 g/L	9.0	8.8	31.1
Non-Haematological Toxicity			
<i>Body as a whole:</i>			
<i>Fluid retention</i>			
<i>Regardless of premedication:</i>			
All	61.0	47.0	39.3
Severe	9.3	6.9	8.2
<i>3 day premedication:</i>			
All	-	64.1	66.7
Severe	-	6.5	33.3
<i>Infections:</i>			
overall	20.0	21.6*	32.8
Severe	1.3	6.1	16.4
<i>Asthenia</i>			
All	56.0	61.8	52.5
Severe	5.0	12.8	24.6
Myalgia	10.7	18.9	16.4

Arthralgia	0.0	9.2	6.6
<i>Neurological</i>			
<i>Neurosensory:</i>			
All	37.0	49.3	34.4
Severe	1.3	4.3	0.0
<i>Neuromotor</i>			
All	4.0	13.8	6.6
Severe	0.0	3.6	1.6
<i>Cutaneous</i>			
Skin:			
All	45.3	47.6	54.1
Severe	1.3	4.8	9.8
Nail disorders	50.0	30.6	23.0
Alopecia	92.0	75.8	62.3
<i>Gastrointestinal</i>			
Nausea	44.0	38.9	37.7
Diarrhoea	28.0	38.7	32.8
Vomiting	21.0	22.3	23.0
Stomatitis			
All	10.7	41.7	49.2
Severe	2.6	5.5	13.0
Mucositis	40.0	-	-
<i>Infusion site effects</i> consisting of hyperpigmentation, inflammation, redness or dryness of skin, phlebitis or extravasation and swelling of the vein	5.6	4.4	3.3

* Normal liver function tests (LFTs): transaminase ≤ 1.5 times upper limit of normal or alkaline phosphatase ≤ 2.5 times upper limit of normal or isolated elevations of transaminase or alkaline phosphatase up to five times upper limit of normal

~ ANC - Absolute neutrophil count

Thirty-five toxic deaths (1.7%) were reported in the 2045 patients with normal baseline liver function tests treated with docetaxel as monotherapy at the initially planned dose of 100mg/m². Septic deaths (neutropenic infections, pneumonia or sepsis) accounted for 80% of the toxic deaths. The incidence of toxic deaths was higher (9.8%) in patients with elevated baseline LFTs.

Hypersensitivity effects generally occur within a few minutes of the start of infusion and were generally mild to moderate. Frequently reported symptoms

were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and medicine fever or chills (see **PRECAUTIONS**).

Haematological

Bone marrow suppression and other haematologic adverse effects to docetaxel include:

Neutropenia (in patients who did not receive G-CSF), the most frequent adverse effect, was reversible and not cumulative. The median day to nadir was 7 days and the median duration of severe neutropenia was 7 days.

Febrile neutropenia and severe infections associated with neutrophil counts $<0.5 \times 10^9/L$, infectious episodes (severe including sepsis pneumonia, fatal in 1.7%), occurred. Thrombocytopenia, bleeding episodes (rarely associated with severe thrombocytopenia) and anaemia (severe) were also reported.

Disseminated intravascular coagulation (DIC), often in association with sepsis, or multi-organ failure, has been reported.

Neurologic

Mild to moderate neuro-sensory signs and/or symptoms occurred in 50% of the patients. Severe neurosensory symptoms (paresthesia, dysesthesia, pain including burning) were observed in 4.1% of metastatic breast cancer patients, and resulted in treatment discontinuation in 2%. Neuro-motor events (13.8% with 4% severe) were mainly characterised by weakness. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued. Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event were available had spontaneous reversal of symptoms with a median of 81 days from onset (range 0 to 741 days).

Rare cases of convulsion or transient loss of consciousness have been observed with docetaxel administration. These effects sometimes appear during the infusion of the medicine.

Hepatic

In patients treated at $100\text{mg}/\text{m}^2$ as a single agent, increase in serum levels of AST, ALT, bilirubin and alkaline phosphatase greater than 2.5 the ULN were observed in less than 5% of patients. Very rare cases of hepatitis have been reported.

Breast Cancer

Docetaxel in Combination with Capecitabine

The adverse effect profile is consistent with the known toxicities of monotherapy treatments.

The most frequent treatment-related adverse effects ($\geq 5\%$) reported in the phase III clinical trial for docetaxel in combination with capecitabine in patients

with locally advanced and/or metastatic breast cancer (n=251) are shown in the table below.

The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (20%) in the monotherapy arm discontinued from the trial because of adverse effects. The percentages of patients requiring dose reductions due to adverse effects were 65% in the combination arm and 36% in the monotherapy arm.

Treatment-related adverse effects reported in ≥5% of patients treated with docetaxel in combination with capecitabine

Body system Adverse effect	Capecitabine 1250mg/m ² twice daily with docetaxel 75mg/m ² /3 weeks (n=251)				Docetaxel 100mg/m ² /3 weeks (n=255)			
	All %	Grades	Grade %	3/4	All %	Grades	Grade %	3/4
Gastrointestinal								
Stomatitis	67		18		42		5	
Diarrhoea	64		14		45		5	
Nausea	43		6		35		2	
Vomiting	33		4		22		1	
Constipation	14		1		12		-	
Abdominal pain	14		2		9		1	
Dyspepsia	12		-		5		<1	
Abdominal pain upper	9		-		6		1	
Dry mouth	5		-		4		-	
Cutaneous								
Hand-foot syndrome	63		24		7		1	
Alopecia	41		6		42		7	
Nail disorder	14		2		15		-	
Dermatitis	8		-		9		1	
Rash erythematous	8		<1		4		-	
Nail discoloration	6		-		4		<1	
Onycholysis	5		1		5		1	
General								
Asthenia	23		3		22		5	
Pyrexia	21		1		29		<1	
Fatigue	21		4		25		5	
Weakness	13		1		9		2	

Pain in limb	9	<1	8	<1
Lethargy	6	-	5	1
Pain	6	-	2	-
Neurologic				
Taste disturbance	15	<1	14	<1
Paresthesia	11	<1	15	1
Dizziness	9	-	6	<1
Headache	7	<1	8	1
Peripheral neuropathy	5	-	10	1
Cardiovascular				
Lower limb oedema	14	1	12	1
Sore throat	11	2	7	<1
Dyspnoea	7	1	9	<1
Cough	6	<1	9	-
Epistaxis	5	<1	5	-
Metabolism				
Anorexia	12	1	10	1
Decreased appetite	10	-	4	-
Dehydration	8	2	5	1
Decreased weight	6	-	4	-
Eye				
Increased lacrimation	12	-	5	-
Musculoskeletal				
Myalgia	14	2	24	2
Arthralgia	11	1	18	2
Back pain	7	1	6	1
Infection				
Oral candidiasis	6	<1	7	<1
Haematologic*				
Decreased haemoglobin	13	4	11	4
Neutropenic fever	21	16	21	21
Leucopenia	3	3	2	2
Biochemical laboratory				

abnormalities*				
Increased alkaline phosphatase	51	1	48	2
Increased bilirubin	23	9	6	3
Increased AST	42	3	37	4
Increase ALT	30	2	30	2
Serum creatinine	7	<1	4	-

* Grades according to National Cancer Institute of Canada Toxicity Criteria, version 1, Dec 1994 were used

Frequent Grade 3 and 4 Laboratory Abnormalities were:

Adverse Event	capecitabine (n=251)	with	docetaxel
Laboratory Abnormalities	Grade		3/4
	%		
Neutropenia	63		
Anaemia	10		
Thrombocytopenia	3		
Hyperbilirubinaemia	9		

Rare or uncommon adverse effects, as described for capecitabine monotherapy, can be expected for combination therapy as well. Refer to capecitabine Product Information for adverse effects which are at least remotely related to capecitabine occurring in <5% of patients treated with capecitabine in combination with docetaxel.

Adjuvant Treatment of Breast Cancer

Combination with Doxorubicin and Cyclophosphamide

The following table presents clinically important treatment-emergent adverse events (TEAEs) observed in 744 patients, who were treated with docetaxel 75mg/m² every 3 weeks in combination with doxorubicin and cyclophosphamide and 736 patients, treated with the comparator study medicines.

Clinically important treatment-emergent adverse events (TEAEs) considered related to study treatment in patients receiving Docetaxel in combination with doxorubicin and cyclophosphamide

Body system	Adverse effect	Docetaxel 75 mg/m ² + Doxorubicin 50 mg/m ² + Cyclophosphamide 500 g/m ² n=744		Fluorouracil 500 mg/m ² + Doxorubicin 50 mg/m ² + Cyclophosphamide 500 g/m ² n=736	
		All Grades (%)	Grade 3 / 4 (%)	Any (%)	Grade 3 / 4 (%)

Cutaneous				
Alopecia	97.7	N/A	97.1	N/A
Skin toxicity	18.4	0.7	10.9	0.3
Nail disorder	18.4	0.4	13.9	0.1
Haematologic				
Anaemia	91.5	4.3	71.7	1.6
Neutropenia	71.4	65.5	82.0	49.3
Thrombocytopenia	39.4	2.0	27.7	1.2
Febrile neutropenia	24.7	N/A	2.5	N/A
Neutropenic infection	12.1	N/A	6.3	N/A
Gastrointestinal				
Nausea	80.4	5.1	87.4	9.5
Stomatitis	69.1	7.1	52.6	2.0
Vomiting	42.6	4.3	58.2	7.3
Diarrhoea	30.9	3.2	23.5	1.0
Constipation	22.6	0.4	21.5	1.2
Abdominal pain	7.3	0.5	3.3	0.0
General				
Asthenia	79.2	11.0	69.4	5.2
Fever in absence of infection	43.1	1.2	13.2	0.0
Infection*	27.2	3.2	17.4	1.4
Peripheral oedema	26.7	0.4	7.2	0.0
Hypersensitivity effects	10.5	1.1	2.2	0.0
Lymphoedema	0.3	0.0	0.0	0.0
Gynaceologic				
Amenorrhoea	57.6	N/A	48.1	N/A
Neurologic				
Taste Perversion	27.4	0.7	15.1	0.0
Neuropathy sensory	23.8	0.0	7.9	0.0
Neuro-cortical	2.8	0.3	3.9	0.3
Neuropathy motor	2.8	0.0	1.5	0.0
Neuro-cerebellar	1.1	0.1	0.8	0.0
Syncope	0.5	0.0	0.4	0.0
Musculoskeletal				
Myalgia	22.8	0.8	8.0	0.0
Arthralgia	15.1	0.4	5.7	0.3
Cardiovascular				
CHF	0.0	1.6	0.0	0.5
Vasodilatation	20.3	0.9	15.9	0.4

Cardiac dysrhythmias**	3.9	0.1	2.9	0.3
Hypotension	1.5	0.0	0.5	0.0
Phlebitis	0.7	0.0	0.4	0.0
Metabolic				
Anorexia	19.9	2.2	16.4	1.2
Weight gain or loss	15.2	0.3	9.2	0.0
Eye				
Lacrimation disorder	9.8	0.1	6.4	0.0
Conjunctivitis	4.6	0.3	6.0	0.1
Respiratory				
Cough	3.1	0.0	2.2	0.1

N/A not applicable

* there was no septic death in either treatment arms

** one patient died due to heart failure in DAC arm

Of the 744 patients treated with DAC, 33.1% experienced severe TEAEs. Dose reductions due to haematologic toxicity occurred in 1% of cycles in DAC arm. Six percent of patients treated with DAC discontinued treatment due to adverse events; fever in the absence of infection and allergy being the most common reasons for withdrawal. Two patients died within 30 days of their last study treatment; 1 death was considered to be related to study medicine.

Fever and Infection

Fever in the absence of infection was seen in patients and infection was seen in patients. There were no septic deaths.

Gastrointestinal Events

In addition to gastrointestinal events reflected in the above table, four patients were reported to have colitis/enteritis/large intestine perforation in the DAC arm. Two of these patients required treatment discontinuation; no deaths due to these events occurred.

Acute Myeloid Leukaemia/Myelodysplastic Syndrome

At a median follow-up time of 83 months, AML occurred in three of 744 (0.4%) patients who received docetaxel, doxorubicin and cyclophosphamide and in one of 736 (0.1%) patients who receive fluoracil, doxorubicin and cyclophosphamide.

Cardiovascular Events

The following cardiovascular events were reported: dysrhythmias, all Grades (3.9%), hypotension, all Grades (1.5%) and CHF (2.3% at 70 months median follow-up). One patient died due to heart failure.

Other Persistent Effects

The following events were observed to be ongoing at the median follow-up time of 55 months: alopecia, amenorrhea, neurosensory and peripheral oedema.

Combination with Doxorubicin, Cyclophosphamide and Trastuzumab and with Carboplatin and Trastuzumab (HER2+)

Adverse Events (AEs) Related to Study Treatment, Occurring at Any Time During the Study: Safety population (incidence of $\geq 5\%$ for non-cardiac AEs; incidence of $\geq 1\%$ for cardiac AEs)

Adverse Event (NCI-CTC term)	AC-T n=1050		AC-TH n=1068		TCH n=1056	
	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)	Overall n (%)	Grade 3/4 n (%)
Alopecia	1029 (98.0)	0	1047 (98.0)	0	1012 (95.8)	0
Haemoglobin ^a	957 (91.1)	25 (2.4)	1036 (97.0)	34 (3.2)	1017 (96.3)	61 (5.8)
Nausea	916 (87.2)	61 (5.8)	931 (87.2)	57 (5.3)	853 (80.8)	49 (4.6)
Leucocytes ^a	878 (83.6)	540 (51.4)	929 (87.0)	643 (60.2)	877 (83.0)	507 (48.0)
Neutrophils ^a	859 (81.8)	664 (63.2)	922 (86.3)	761 (71.3)	859 (81.3)	696 (65.9)
Fatigue	844 (80.4)	71 (6.8)	868 (81.3)	71 (6.6)	849 (80.4)	73 (6.9)
Stomatitis/pharyngitis	663 (63.1)	38 (3.6)	694 (65.0)	32 (3.0)	547 (51.8)	15 (1.4)
Vomiting	571 (54.4)	61 (5.8)	591 (55.3)	68 (6.4)	416 (39.4)	32 (3.0)
SGPT (ALT) ^a	506 (48.2)	7 (0.7)	579 (54.2)	19 (1.8)	561 (53.1)	25 (2.4)
Fluid retention ^{a,b}	533 (50.8)	14 (1.3)	558 (52.2)	16 (1.5)	539 (51.0)	15 (1.4)
Myalgia	515 (49.0)	49 (4.7)	544 (50.9)	52 (4.9)	353 (33.4)	15 (1.4)
Diarrhoea	395 (37.6)	31 (3.0)	484 (45.3)	55 (5.1)	589 (55.8)	52 (4.9)
Neuropathy-sensory	464 (44.2)	23 (2.2)	478 (44.8)	20 (1.9)	316 (29.9)	6 (0.6)
SGOT (AST) ^a	426 (40.6)	2 (0.2)	454 (42.5)	9 (0.8)	401 (38.0)	11 (1.0)
Arthralgia	372 (35.4)	30 (2.9)	424 (39.7)	32 (3.0)	230 (21.8)	11 (1.0)
Nail changes	487 (46.4)	0	423 (39.6)	0	246 (23.3)	0
Platelets ^a	296	10 (1.0)	350	13 (1.2)	667	57 (5.4)

	(28.2)		(32.8)		(63.2)	
Irregular menses	353 (33.6)	248 (23.6)	311 (29.1)	213 (19.9)	340 (32.2)	226 (21.4)
Taste disturbance	297 (28.3)	0	290 (27.2)	0	312 (29.5)	0
Constipation	276 (26.3)	6 (0.6)	289 (27.1)	10 (0.9)	232 (22.0)	6 (0.6)
Rash/desquamation	224 (21.3)	16 (1.5)	277 (25.9)	14 (1.3)	241 (22.8)	4 (0.4)
Hot flashes/flushes	220 (21.0)	0	230 (21.5)	0	192 (18.2)	0
Tearing	191 (18.2)	0	228 (21.3)	3 (0.3)	109 (10.3)	0
Alkaline phosphatase ^a	202 (19.2)	3 (0.3)	206 (19.3)	3 (0.3)	215 (20.4)	3 (0.3)
Anorexia	214 (20.4)	5 (0.5)	205 (19.2)	5 (0.5)	222 (21.0)	5 (0.5)
Dyspepsia/heartburn	150 (14.3)	3 (0.3)	203 (19.0)	3 (0.3)	211 (20.0)	4 (0.4)
Headache	163 (15.5)	4 (0.4)	175 (16.4)	6 (0.6)	160 (15.2)	3 (0.3)
Dyspnoea	156 (14.9)	8 (0.8)	166 (15.5)	16 (1.5)	157 (14.9)	18 (1.7)
Weight gain	114 (10.9)	3 (0.3)	159 (14.9)	3 (0.3)	154 (14.6)	2 (0.2)
Infection without neutropenia	105 (10.0)	17 (1.6)	135 (12.6)	20 (1.9)	98 (9.3)	16 (1.5)
Abdominal pain or cramping	108 (10.3)	3 (0.3)	132 (12.4)	4 (0.4)	141 (13.4)	5 (0.5)
Insomnia	106 (10.1)	0	119 (11.1)	1 (0.1)	93 (8.8)	0
Febrile neutropenia	95 (9.0)	95 (9.0)	116 (10.9)	116 (10.9)	103 (9.8)	103 (9.8)
Fever (without neutropenia)	95 (9.0)	3 (0.3)	116 (10.9)	4 (0.4)	70 (6.6)	3 (0.3)
Allergic reaction/hypersensitivity	75 (7.1)	12 (1.1)	105 (9.8)	15 (1.4)	139 (13.2)	26 (2.5)
Bone pain	97 (9.2)	10 (1.0)	104 (9.7)	4 (0.4)	67 (6.3)	1 (0.1)
Infection with Grade 3/4 neutropenia	83 (7.9)	83 (7.9)	98 (9.2)	98 (9.2)	81 (7.7)	81 (7.7)
Pain ^c	98 (9.3)	4 (0.4)	86 (8.1)	4 (0.4)	57 (5.4)	0
Conjunctivitis	84 (8.0)	5 (0.5)	86 (8.1)	0	35 (3.3)	0
Dizziness / light-headedness	65 (6.2)	1 (0.1)	78 (7.3)	7 (0.7)	70 (6.6)	4 (0.4)

Creatinine ^a	39 (3.7)	7 (0.7)	72 (6.7)	5 (0.5)	102 (9.7)	6 (0.6)
Hand-foot skin reaction	84 (8.0)	20 (1.9)	72 (6.7)	15 (1.4)	29 (2.7)	0
Epistaxis	40 (3.8)	0	72 (6.7)	0	104 (9.8)	4 (0.4)
Weight loss	63 (6.0)	0	71 (6.6)	0	56 (5.3)	1 (0.1)
Dry skin	63 (6.0)	0	69 (6.5)	0	41 (3.9)	0
Cough	55 (5.2)	1 (0.1)	66 (6.2)	2 (0.2)	36 (3.4)	0
Rhinitis ^c	49 (4.7)	2 (0.2)	64 (6.0)	1 (0.1)	47 (4.5)	0
Rigors, chills	33 (3.1)	0	63 (5.9)	0	54 (5.1)	0
Infection with unknown ANC	73 (7.0)	73 (7.0)	59 (5.5)	59 (5.5)	38 (3.6)	38 (3.6)
Neuropathy-motor	44 (4.2)	2 (0.2)	57 (5.3)	4 (0.4)	38 (3.6)	3 (0.3)
Bilirubina	52 (5.0)	6 (0.6)	54 (5.1)	4 (0.4)	61 (5.8)	4 (0.4)
Injection site reaction	47 (4.5)	2 (0.2)	50 (4.7)	1 (0.1)	61 (5.8)	2 (0.2)
Mouth dryness	76 (7.2)	0	43 (4.0)	0	29 (2.7)	0
Cardiac left ventricular function	11 (1.0)	1 (0.1)	37 (3.5)	5 (0.5)	15 (1.4)	1 (0.1)
Palpitations	32 (3.0)	0	36 (3.4)	0	47 (4.5)	0
Sinus tachycardia	21 (2.0)	2 (0.2)	19 (1.8)	0	23 (2.2)	0
Hypotension	10 (1.0)	1 (0.1)	10 (0.9)	0	13 (1.2)	2 (0.2)

ACT= doxorubicin, cyclophosphamide and docetaxel

AC-TH = doxorubicin and cyclophosphamide, followed by docetaxel in combination with trastuzumab. TCH = docetaxel in combination with trastuzumab and carboplatin.

^a Regardless of causality

^b Fluid retention AEs are defined as "oedema only", or "weight gain only", or "lung oedema only", or "oedema and weight gain", or "oedema and lung oedema", or "oedema + weight gain + lung oedema". "Fluid retention" corresponds to the NCI-CTC term "oedema".

^c COSTART term

The 3-year cumulative incidence of all symptomatic cardiac events was 2.36% and 1.16% in the AC-TH and TCH arms, respectively (versus 0.52% in the AC-T control arm, see **CLINICAL TRIALS** section). The 3-year cumulative incidence of CHF events (Grade 3 or 4) was 1.9% and 0.4% in the AC-TH and TCH arms, respectively (versus 0.3% in the AC-T control arm).

Prostate Cancer Combination with Prednisone or Prednisolone

The adverse effect profile is consistent with the known safety profile of docetaxel.

The table below provides the percentage of subjects with clinically important treatment-emergent adverse events (TEAEs) and haematological toxicities related to study treatment, reported in the phase III clinical trial for docetaxel 75mg/m² q3w and mitozantrone q3w in combination with prednisone (or prednisolone).

Clinically important treatment-emergent adverse events related to study medication

	Docetaxel 75 mg/m ² every 3 weeks (n=322)		Mitozantrone 12 mg/m ² every 3 weeks (n=335)	
	Grade 3/4	Any	Grade 3/4	Any
Cutaneous				
Alopecia	N/A*	65.1	N/A*	12.5
Nail changes	0.0	28.3	0.0	6.6
Rash/desquamation	0.3	3.3	0.0	0.9
Haematologic				
Neutropenia	32.0	40.9	21.7	48.2
Anaemia	4.9	66.5	1.8	57.8
Thrombocytopenia	0.6	3.4	1.2	7.8
Epistaxis	0.0	3.0	0.0	0.6
Febrile neutropenia	N/A	2.7	N/A*	1.8
General				
Fatigue	3.9	42.8	2.7	26.6
Infection	3.3	12.0	2.1	4.8
Stomatitis/pharyngitis	0.9	17.8	0.0	7.8
Fluid retention	0.6	24.4	0.3	4.5
Allergic reaction	0.6	6.9	0.0	0.3
Anorexia	0.6	12.7	0.0	11.6
Gastrointestinal				
Nausea	2.4	35.5	0.9	28.7
Diarrhoea	1.2	24.1	0.9	4.2
Vomiting	1.2	13.3	0.6	7.2
Neurologic				
Neuropathy sensory	1.2	27.4	0.0	2.1
Taste disturbance	0.0	17.5	0.0	6.3
Neuropathy motor	0.0	3.9	0.0	0.9
Respiratory				
Dyspnoea	0.6	4.5	0.3	3.3
Cough	0.0	1.2	0.0	0.9
Eye				
Tearing	0.6	9.3	0.0	1.5
Musculoskeletal				
Myalgia	0.3	6.9	0.0	3.3
Arthralgia	0.3	3.0	0.0	0.6

Cardiovascular				
Abnormal cardiac left ventricular function	0.3	3.9	0.9	19.1

* NA: not applicable.

Head and Neck Cancer

Combination with Cisplatin and Fluorouracil

The following table summarises the safety data obtained in 174 patients (TAX 323) and 251 patients (TAX 324) with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who were treated with docetaxel 75mg/m² in combination with cisplatin and fluorouracil.

Clinically Important Treatment-Related Adverse Events in Patients with SCCHN Receiving docetaxel in Combination with Cisplatin and Fluorouracil

	TAX323: docetaxel 75mg/m² + cisplatin 75mg/m² + fluorouracil 750mg/m² (n=174)		TAX 324: docetaxel 75mg/m² + cisplatin 100mg/m² + fluorouracil 1000mg/m² (n=251)	
Adverse Event	Any %	Grade 3/4 %	Any %	Grade 3/4 %
Blood and lymphatic system				
Neutropenia	93.1	76.3	94.8	83.5
Anaemia	89.1	9.2	90.0	12.4
Thrombocytopenia	23.6	5.2	27.5	4.0
Infection	15.5	6.3	13.1	3.6
Fever in absence of infection	14.4	0.6	26.3	3.6
Neutropenic infection	11.0	0.0	6.5	N/A
Febrile neutropenia*	5.2	0.0	12.1	N/A
Allergy	2.9	0.0	0.4	0.0
Skin and subcutaneous tissue disorders				
Alopecia	79.9	10.9	67.7	4.0
Rash/itch	8.6	0.0	12.7	0.0
Dry skin	5.2	0.0	2.8	0.4
Desquamation	4.0	0.6	2.0	0.0
Fluid retention	20.1	0.0	13.1	1.2
Oedema only	12.6	0.0	12.0	1.2
Weight gain only	5.7	0.0	0.4	0.0
Gastrointestinal disorders				
Nausea	43.7	0.6	75.7	13.9

Stomatitis	42.0	4.0	64.5	20.7
Diarrhoea	29.3	2.9	42.2	6.8
Vomiting	25.9	0.6	56.2	8.4
Taste/sense of smell altered	10.3	-	19.5	0.4
Constipation	6.9	0.0	13.9	0.4
Oesophagitis/dysphagia/odynophagia	5.7	0.6	21.9	12.0
Gastrointestinal pain/cramping	5.2	-	6.0	1.2
Heartburn	4.0	-	8.8	0.8
Gastrointestinal bleeding	1.1	0.6	2.0	0.4
Nervous system disorders				
Neurosensory	16.7	0.6	11.6	1.2
Neuromotor	-	-	7.2	0.4
Dizziness	1.1		9.6	2.0
Cardiac disorders				
Myocardial Ischaemia	1.7	1.7	0.8	0.8
Cardiac dysrhythmia	0.6	0.6	3.2	0.2
Vascular disorders				
Venous	1.1	0.6	0.8	0.4
Metabolism and nutrition disorders				
Anorexia	15.5	0.6	37.8	12.0
Weight loss	9.8	0	11.2	0.0
Eye disorders				
Tearing	1.7	0	1.6	0.0
Conjunctivitis	1.1	0	0.8	0.0
Ear and labyrinth disorders				
Altered hearing	5.7	0	11.2	1.2
Musculoskeletal, connective tissue and bone disorders				
Myalgia	6.3	0.6	5.2	0.4
General disorders and administration site conditions				
Lethargy	37.9	3.4	58.6	4.0
Cancer pain	1.1	0.6	3.2	1.2

* Febrile neutropenia: Grade ≥ 2 fever concomitant with Grade 4 neutropenia requiring i.v. antibiotics and/or hospitalisation

Clinically important TEAEs were determined based upon frequency, severity, and clinical impact of the adverse event

Post Marketing Adverse Effects

The following information relates to serious events observed following the marketing of docetaxel. Voluntary reports of serious adverse events that have been received since market introduction (without causal relationship) that are not listed previously are cited below. Frequency estimates are as follows: common $\geq 1-10\%$, uncommon 0.1-1%; rare 0.01-0.1%; very rare $<0.01\%$.

Body as a Whole

Uncommon: chest pain, diffuse pain.

Rare: abdominal pain.

Very rare: radiation recall phenomenon.

Hypersensitivity

Rare: cases of anaphylactic shock have been reported.

Very rare: these cases resulted in a fatal outcome in patients who received premedication.

Cutaneous

Very rare: cases of cutaneous lupus erythematosus and bullous eruptions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and scleroderma-like changes have been reported. Multiple factors such as concomitant infections, concomitant medications and underlying disease may have contributed to the development of these effects.

Severe nail disorders characterised by hypo- or hyperpigmentation, and infrequently onycholysis and pain.

Fluid retention

Rare: dehydration and pulmonary oedema have been reported.

Gastrointestinal

Rare: constipation, oesophagitis and taste perversion, gastrointestinal haemorrhage, dehydration as a consequence of gastrointestinal events.

Very rare: duodenal ulcer, ileus and intestinal obstruction, gastrointestinal perforation, neutropenic enterocolitis, colitis including ischemic colitis.

Neurologic

Rare: confusion, seizures, transient loss of consciousness. These effects sometimes occur during infusion of the medicine.

Cardiovascular

Common: hypertension, hypotension.

Uncommon: cardiac arrhythmia, congestive heart failure.

Rare: atrial fibrillation, syncope, tachycardia.

Very rare: deep vein thrombosis, myocardial infarction, ECG abnormalities, thrombophlebitis, pulmonary embolism.

Hepatic

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

Ear and labyrinth disorders

Rare: cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic medicines.

Eye disorders

Rare: cases of lacrimation with or without conjunctivitis have been reported and very rare cases of lacrimal duct obstruction resulting in excessive tearing have been reported primarily in patients receiving other anti-tumour agents concomitantly.

Cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during medicine infusion and in association with hypersensitivity have been reported. These were reversible upon discontinuation of the infusion.

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea.

Rare: Acute respiratory distress syndrome, interstitial pneumonia, acute pulmonary oedema, pulmonary fibrosis and radiation recall phenomena have rarely been reported. Rare cases of radiation pneumonitis have been reported in patients receiving concomitant therapy.

Haematological and lymphatic disorders

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

Disseminated intravascular coagulation (DIC), often in association with sepsis, or multiorgan failure, has been reported

Urogenital

Rare: renal insufficiency and renal failure associated with concomitant nephrotoxic medicines have been reported.

Other

Common: generalised or localised pain including chest pain without cardiac or respiratory involvement.

DOSAGE AND ADMINISTRATION

Breast Cancer

Monotherapy

The recommended dosage of Docetaxel Ebewe is 75 to 100mg/m² administered as a one-hour infusion every three weeks (see Preparation for the Intravenous Administration). A dose of 100mg/m² of docetaxel has been shown to result in a moderate increase in response rates compared with 75mg/m² but is associated with greater toxicity.

Combination with Capecitabine

The recommended dosage of Docetaxel Ebewe is 75mg/m² administered as a one-hour infusion every three weeks when combined with capecitabine administered orally at 1,250mg/m² twice daily (within 30 minutes after the end of a meal) for two weeks followed by a 1-week rest period, given as 3-week cycles. Refer to capecitabine Product Information for capecitabine dose calculation according to body surface area.

Adjuvant Treatment of Breast Cancer

Combination with Doxorubicin and Cyclophosphamide

The recommended dose of Docetaxel Ebewe in the adjuvant treatment of breast cancer is 75mg/m² administered 1 hour after doxorubicin 50mg/m² and cyclophosphamide 500mg/m² every 3 weeks for a total of six cycles (see also Dosage Adjustments During Treatment and **PRECAUTIONS**, Haematology).

Combination with Trastuzumab following Doxorubicin and Cyclophosphamide (HER2+)

- AC-TH:

AC (cycles 1 - 4): doxorubicin (A) 60 mg/m² followed by cyclophosphamide (C) 600 mg/m² administered every three weeks for 4 cycles.

TH (cycles 5 - 8): docetaxel (T) 100 mg/m² administered every three weeks for 4 cycles, and trastuzumab (H) administered weekly according to the following schedule:

- Cycle 5 (starting three weeks after the last cycle of AC):

Day 1: trastuzumab 4 mg/kg (loading dose)

Day 2: docetaxel 100 mg/m²

Days 8 and 15: trastuzumab 2 mg/kg

- Cycles 6 - 8:

Day 1: docetaxel 100 mg/m² and trastuzumab 2 mg/kg

Days 8 and 15: trastuzumab 2 mg/kg

Three weeks after day 1 of cycle 8: trastuzumab 6 mg/kg is given every three weeks.

Trastuzumab is administered for a total duration of 1 year.

Combination with Carboplatin and Trastuzumab (HER2+)

- TCH:

TCH (cycles 1 - 6): docetaxel (T) 75 mg/m² and carboplatin (C) at AUC of 6 mg/mL/min administered every three weeks and trastuzumab (H) administered weekly according to the following schedule:

- Cycle 1:

Day 1: trastuzumab 4 mg/kg (loading dose)

Day 2: docetaxel 75 mg/m² and carboplatin at AUC of 6 mg/mL/min

Days 8 and 15: trastuzumab 2 mg/kg

- Cycles 2 - 6:

Day 1: docetaxel 75 mg/m² followed by carboplatin at AUC of 6 mg/mL/min and trastuzumab 2 mg/kg

Days 8 and 15: trastuzumab 2 mg/kg

Three weeks after day 1 of cycle 6: trastuzumab 6 mg/kg is given every three weeks.

Trastuzumab is administered for a total duration of 1 year.

Non-Small Cell Lung Cancer

The recommended dosage of Docetaxel Ebewe is 75 to 100mg/m² administered as a one-hour infusion every three weeks (see Preparation for the Intravenous Administration). A dose of 100mg/m² of docetaxel has been shown to result in a moderate increase in response rates compared with 75mg/m² but is associated with greater toxicity.

Prostate Cancer

The recommended dosage of Docetaxel Ebewe for prostate cancer is 75mg/m² administered as a one-hour infusion every three weeks. Prednisone or prednisolone 5mg orally twice daily is administered continuously, commencing day 1 and continuing through each cycle.

Head and Neck Cancer

Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. For cisplatin and fluorouracil dose modifications, see manufacturers' Product Information.

Induction chemotherapy followed by radiotherapy (TAX 323)

For the induction treatment of locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of Docetaxel Ebewe is 75mg/m² as a one-hour infusion followed by cisplatin 75mg/m² over one hour, on day 1, followed by fluorouracil as a continuous infusion at 750mg/m² per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy.

Induction chemotherapy followed by chemoradiotherapy (TAX 324)

For the induction treatment of patients with locally advanced (unresectable, low surgical cure, or organ preservation) SCCHN, the recommended dose of Docetaxel Ebewe is 75mg/m² as a 1-hour intravenous infusion on day 1, followed by cisplatin 100mg/m² administered as a 30-minute to 3-hour infusion, followed by fluorouracil 1000mg/m² 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.

Premedication in Breast, Non-Small Cell Lung, and Head and Neck Cancers

A premedication consisting of an oral corticosteroid, such as dexamethasone 16mg per day (e.g. 8mg twice daily) for 3 days starting one day prior to docetaxel administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Premedication in Prostate Cancer

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

Dosage Adjustments During Treatment

Docetaxel Ebewe should be administered when the neutrophil count is ≥ 1.5 cells $\times 10^9/L$.

In Patients Treated at 75mg/m²

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells $\times 10^9/L$ for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during Docetaxel Ebewe therapy should have the dosage of Docetaxel Ebewe reduced from 75mg/m² to 55mg/m² (or to 60mg/m² for adjuvant therapy for breast cancer). If the patient continues to experience these reactions at 55mg/m² (or at 60mg/m²), the treatment should be discontinued.

In Patients Treated at 100mg/m²

Patients who experienced either febrile neutropenia, neutrophil < 0.5 cells $\times 10^9/L$ for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during Docetaxel Ebewe therapy should have the dosage of Docetaxel Ebewe reduced from 100mg/m² to 75mg/m². If the patient continues to experience these reactions at 75mg/m², the dosage should either be decreased from 75mg/m² to 55mg/m², or the treatment should be discontinued.

Patients Treated with Docetaxel Ebewe in Combination with Capecitabine

For capecitabine dose modifications when combined with Docetaxel Ebewe, see capecitabine Product Information.

For patients developing the first appearance of a Grade 2 toxicity which persists at the time of the next Docetaxel Ebewe/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 a Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, then resume treatment with Docetaxel Ebewe 55mg/m².

For any subsequent appearances of toxicities, or any Grade 4 toxicities, discontinue the Docetaxel Ebewe dose.

Patients Treated with Docetaxel Ebewe in Combination with Doxorubicin and Cyclophosphamide (TAC)

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

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive G-CSF in all subsequent cycles. Patients who continue to experience this reaction should remain on G-CSF and have their Docetaxel Ebewe dose reduced to 60mg/m². If G-CSF is not used, the Docetaxel Ebewe dose should be reduced from 75 to 60mg/m². Patients who experience Grade 3 or 4 stomatitis should have their dose decreased to 60mg/m².

Patients Treated with Docetaxel Ebewe in AC-TH or TCH

Patients who received AC-TH or TCH adjuvant therapy for operable breast cancer whose tumours overexpress HER2 and who experience an episode of febrile neutropenia or infection should receive prophylactic G-CSF in all subsequent cycles. For a second episode of febrile neutropenia or infection, patients should continue prophylactic G-CSF, and Docetaxel Ebewe will be reduced from 100 mg/m² to 75 mg/m² (in the AC-TH regimen); Docetaxel Ebewe will be reduced from 75 mg/m² to 60 mg/m² (in the TCH regimen).

However, in clinical practice neutropenia could occur in cycle 1. Thus, G-CSF should be used in consideration of the neutropenic risk of the patient and current recommendations. Depending on the treatment regimen, patients who experience Grade 3 or 4 stomatitis should have their dose decreased from 100 mg/m² to 75 mg/m² (in the AC-TH regimen) or from 75 mg/m² to 60 mg/m² (in the TCH regimen).

Patients Treated with Docetaxel Ebewe in Combination with Cisplatin and Fluorouracil in Head and Neck Cancer

Patients treated with Docetaxel Ebewe in combination with cisplatin and fluorouracil must receive antiemetics and appropriate hydration according to current institutional guidelines. G-CSF should be administered to mitigate the risk of complicated neutropenia.

If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the Docetaxel Ebewe dose should be reduced from 75 to 60 mg/m². If subsequent episodes of complicated neutropenia occur the Docetaxel Ebewe dose should be reduced from 60 to 45 mg/m².

In case of Grade 4 thrombocytopenia the Docetaxel Ebewe dose should be reduced from 75 to 60 mg/m². Patients should not be retreated with subsequent cycles of Docetaxel Ebewe until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level > 100 000 cells/m³. Discontinue treatment if these toxicities persist.

For cisplatin and fluorouracil dosage and administration, see the relevant Product Information leaflet.

Recommended Dose Modifications for Toxicities in Patients Treated with Docetaxel Ebewe in Combination with Cisplatin and Fluorouracil

Toxicity	Dosage adjustment
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Diarrhoea grade 3	1 st episode: reduce fluorouracil (FU) dose by 20% 2 nd episode: then reduce Docetaxel Ebewe dose by 20%
Diarrhoea grade 4	1 st episode: reduce Docetaxel Ebewe and fluorouracil (FU) doses by 20% 2 nd episode: discontinue treatment
Stomatitis/mucositis grade 3	1 st episode: reduce fluorouracil (FU) dose by 20% 2 nd episode: stop fluorouracil (FU) only, at all subsequent cycles 3 rd episode: reduce Docetaxel Ebewe dose by 20%
Stomatitis/mucositis grade 4	1 st episode: stop fluorouracil (FU) only, at all subsequent cycles 2 nd episode: reduce Docetaxel Ebewe dose by 20%

Special Populations

Patients with Hepatic Impairment

In Patients Treated at 75mg/m²

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

In Patients Treated at 100mg/m²

Based on the pharmacokinetic data, in patients who have both elevations of transaminase values [ALT and/or AST greater than 1.5 times the upper limit of normal range (ULN)] and increases in alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of docetaxel is 75mg/m² (see **Pharmacokinetics**). For those patients with increased serum bilirubin and/or values >3.5 times the ULN for ALT and AST and >6 times the ULN for alkaline phosphatase, no dose-reduction can be recommended and docetaxel should not be used unless strictly indicated.

Paediatric Use

The safety and effectiveness of docetaxel in children have not been established.

Use in the Elderly

Based on the population pharmacokinetics, there are no special instructions for the use in elderly.

For capecitabine dosage reduction when combined with Docetaxel Ebewe, see capecitabine Product Information.

Preparation for the Intravenous Administration

More than one vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding volume containing docetaxel 10

mg/mL from the appropriate number of vials using a graduated syringe fitted with a needle. For example, a dose of docetaxel 140 mg would require 14 mL docetaxel solution.

The concentrate must be diluted before use.

To minimise the potential for precipitation of the infusion solution, the use of bags is recommended. Glass bottles are not recommended for use.

The required volume of Docetaxel Ebewe Concentrated Injection must be added via a single injection (one shot) into a 250 mL-infusion bag containing either sodium chloride 0.9% solution or glucose 5% solution for infusion.

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

Mix the infusion bag manually by gentle inversion and rotation in a controlled manner to avoid foaming. Shaking or vigorous agitation has to be avoided during preparation and transportation.

The prepared docetaxel infusion solution is stable for up to 4 hours and should be used within these 4 hours, including storage and the one-hour infusion time to the patient. The infusion should be aseptically administered under room temperature (below 25 °C) and normal lighting conditions.

Docetaxel solution for infusion is an oversaturated solution and therefore can crystallise / precipitate over time. If the vials are stored under refrigeration, allow the required number of vials of Docetaxel Ebewe concentrated injection to stand below 25°C for 5 minutes before use. .

As with all parenteral products, reconstituted docetaxel solution for infusion should be visually inspected prior to use and solutions, if the infusion solution is not clear or appears to have precipitation, it has to be discarded.

Docetaxel solution for infusion should be aseptically administered intravenously as a one-hour infusion under room temperature and normal lighting conditions. To reduce microbiological hazard and the risk of crystallisation of docetaxel from diluted solutions, use as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for not more than 24 hours, including the one-hour infusion time. Chemical and physical in-use stability has been demonstrated at room temperature (below 25 °C) or refrigerated (2°-8°C).

Any residue after infusion should be discarded. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Product is for single use in one patient only. Discard any residue.

Disposal

Docetaxel Ebewe 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 Ebewe concentrate or docetaxel infusion solution comes into contact with the skin, wash immediately and thoroughly with soap and water. If Docetaxel Ebewe concentrate or docetaxel infusion solution comes into contact with mucous membranes, wash immediately and thoroughly with water.

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures.

OVERDOSAGE

In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. There is no known antidote for docetaxel overdose. 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.

There were two reports of overdose. One patient received 150mg/m² and the other received 200mg/m² of docetaxel as a one-hour infusion. They both recovered after experiencing severe neutropenia, mild asthenia, cutaneous reactions and mild paraesthesia.

Contact the Poisons Information Centre (0800 POISON or 0800 764766 for advice on management of overdose).

PRESENTATION AND STORAGE CONDITIONS

Docetaxel Ebewe concentrated injection is a sterile, clear, colourless to pale yellow solution containing: 10mg/mL docetaxel, anhydrous citric acid, macrogol 300, polysorbate 90, ethanol. The following strengths are available:

Docetaxel Ebewe is available in the following presentations:

20mg in 2mL: Cartons of 1 and 5 vials (2mL glass vials)
80mg in 8mL: Cartons of 1 and 5 vials (10mL glass vials)

Store below 25°C. Do not freeze. Protect from light.

NAME AND ADDRESS

Pharmaco (NZ) Limited
4 Fisher Crescent,
Mt Wellington,
AUCKLAND

MEDICINE CLASSIFICATION

Prescription Medicine

DATE OF PREPARATION

27 Oct 2011