

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Taxotere. This scientific discussion has been updated until 1 February 2005. For information on changes after this date please refer to module 8B.

1. Introduction

Taxotere as monotherapy is intended for the treatment of locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. In combination with doxorubicin Taxotere is indicated as first-line treatment for locally advanced or metastatic breast cancer. Taxotere in combination with capecitabine is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Furthermore, Taxotere as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

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

Docetaxel, the active substance of Taxotere, is prepared by semisynthesis using a substance extracted from yew needles, i.e. 10-deacetylbaccatin III (DAB-10).

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

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

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

The main mechanism of resistance is due to overexpression of the cell surface drug transporter glycoprotein GP170 encoded by the MDR1 gene and responsible for multidrug resistance to many structurally similar anticancer drugs: taxoids, vinca-alkaloids, anthracyclines, podophyllotoxins.

2. Chemical, pharmaceutical and biological aspects

Docetaxel, active substance of Taxotere, is prepared by semisynthesis using a substance extracted from the needles of European yew tree and Indian), 10-deacetylbaccatin III (10-DAB).

Taxotere is presented as a concentrate for infusion and is available in two dosage strengths of docetaxel trihydrate corresponding to 20 mg and 80 mg of docetaxel (anhydrous) in polysorbate 80. The composition of the viscous solution is identical for both strengths (40 mg/ml). The accompanying solvent contains 13% ethanol in water for injection.

A study was carried out on the physical stability of the infusion solution to determine a period of use. The overall results showed that respecting the conditions defined the infusion solution remained clear for up to 6 hours after solution, regardless the type of bags (PVC or polyolefin) and infusion vehicle (0.9% NaCl or 5% glucose) used. Taking into account these results, the instructions for the administration of the final infusion solution and for the preparation of the premix solution were simplified as follows:

- Taxotere infusion solution is administered to patients intravenously within the 4 hours including a 1-hour infusion under aseptic conditions. The maximum concentration acceptable was defined to be 0.74-mg/ml docetaxel. The infusion solution is prepared by diluting the required premix volume (i.e. 10 mg docetaxel/ml) into a 250 ml bag or bottle containing 0.9% sodium chloride solution or 5% glucose solution.
- The premix itself is obtained by manually mixing the content of one vial of Taxotere concentrate for infusion (20 or 80 mg) with the content of one vial of the correspondent specific solvent. The premix solution, which contains 10-mg/ml docetaxel, should be used immediately to prepare the infusion solution. However, the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between +2°C and +8°C or at room temperature. The reconstitution should be made under aseptic conditions.

The original formulation of Taxotere (formulation 2) has been replaced by formulation 3. The quality of the current polysorbate 80 DF has been optimised, resulting in an improvement in stability. This resulted in a change in the specifications, an extension of the shelf life and a change in the storage conditions of the finished medicinal product. As a consequential change, analytical methods of both polysorbate DF and Taxotere concentrate have been adapted.

3. Toxicopharmacological aspects

An extensive preclinical programme was carried out in different laboratories in Europe, North America and Japan. Overall the results were consistent with those obtained from similar studies performed in other laboratories.

The toxicology file clearly defined the acute toxicity in tested species and the lack of cumulative toxicity in animals but failed in identifying some of the side effects observed in humans such as skin toxicity and fluid retention syndrome despite the use of “strategy mimicking studies”.

Docetaxel has been shown to be mutagenic in cytogenic tests, as predicted based on its pharmacological activity.

No carcinogenicity studies were performed, which is acceptable regarding the intended use of Taxotere.

Docetaxel has been shown to be both embryotoxic and foetotoxic in rabbits and rats and to reduce fertility in rats. Thus docetaxel is contraindicated in pregnant women.

No major objection was raised to this part of the dossier.

In order to support the change in formulation, additional toxicity studies have been carried out. The results of these studies indicate that formulation 3 had a similar toxicity profile as formulation 2 and, in particular, had no intravenous, paravenous or intra-arterial irritation potential, and that it was compatible *in vitro* with human plasma, serum and blood under conditions similar to that of clinical use.

Pharmacokinetics

The preclinical pharmacokinetic studies supplied sufficient information on plasma clearance, tissue and tumour distribution and metabolism of docetaxel and support the schedule and doses used in early clinical studies.

The plasma protein binding of docetaxel is high (more than 95%). Potential interactions with tightly protein-bound drugs were investigated and no change in the protein binding of docetaxel was found. *In vitro* potential interactions between docetaxel and compounds that induce, inhibit or are metabolised (and thus may inhibit the enzyme competitively) by cytochrome P450-3A such as ciclosporine, terfenadine and ketoconazole were observed. These findings have been adequately addressed in the SPC.

4. Clinical aspects

Clinical Pharmacology

The pharmacokinetics in humans has deserved extensive studies, of which a large part was dedicated to population pharmacokinetics.

Pharmacokinetic (PK) parameters for docetaxel are adequately defined, and show little variability in the tested population (even a coefficient of variation of 55% for plasma clearance is in the low range of the variations usually observed). A large number of patients were included in the studies; therefore one cannot expect significant modifications in relation to age in adult patients, to tumour type or tumour burden. However, more variability is to be expected with patients with poor performance status and/or abnormal liver function tests.

The impact of altered performance status, denutrition and low plasma protein level can be suspected but will have to be studied in a representative population of patients.

PK parameters were not a prognostic factor according to 2 studies investigating PK and efficacy in patients with breast cancer (168 patients) and in patients with non-small cell lung cancer (151 patients).

PK/PD did not establish, as expected from the limited variability of PK parameters, any relation between PK parameters and efficacy

Relation of PK to neutropenia was studied in 534 patients: no correlation was observed.

Relation of PK to fluid retention was analysed using a COX model in 575 patients; actuarial risk for fluid retention was slightly increased in patients with low plasma clearance. However, stability of PK in relation to fluid-retention was not studied.

There were no formal clinical studies to evaluate *in vivo* the drug interactions of docetaxel. *In vitro* studies showed, however, that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A, such as ciclosporine, terfenadine, ketoconazole.

Five phase I studies with Taxotere in combination with other anticancer agents were conducted to define the dose limit toxicities, the maximum tolerated dose and the recommended dose of Taxotere when combined with 5-fluorouracil, cyclophosphamide, doxorubicin and vinorelbine. The overall preliminary results submitted for these studies showed that Taxotere could be safely combined with vinorelbine, 5-fluorouracil both bolus and continuous infusion, cyclophosphamide and doxorubicin. The safety profile of the combinations tested did not show a qualitative and quantitative increase in the adverse effects observed with Taxotere as monotherapy.

The pharmacokinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model. Docetaxel is approximately 94% protein bound and is eliminated in both the urine and faeces following a metabolism conducted by the CYP3A4 isoenzyme. As prednisone and prednisolone are known to induce moderately CYP3A4, PK of docetaxel in combination with prednisone was studied as part of the pivotal trial in the prostate cancer indication. The results of this pharmacokinetic assessment were similar for docetaxel alone and for the combination with prednisone. No statistical difference was observed for total clearance between the two periods with or without concomitant prednisone (p-value= 0.9808).

A pharmacokinetic interaction study XRP6976D-1001 demonstrated that there was no pharmacokinetic interaction during the co-administration of doxorubicin cyclophosphamide, and docetaxel.

Clinical experience

Efficacy

Locally advanced or metastatic breast cancer after failure of prior chemotherapy

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

The overall response rate (ORR) was 56% in the anthracycline resistant patients with a 4.4% complete response rate (CR). A 46% ORR was observed in the anthracycline refractory patients with 7.3% CR. The median duration of response was 27 weeks in the anthracycline resistant patients and 28 weeks in the anthracycline refractory patients. The median survival time was 11 months in the anthracycline-resistant patients.

There was a high response rate in patients with visceral metastases, 53.1% in the 49 anthracycline resistant patients in whom visceral metastases were present.

In anthracycline resistant patients, a significant response rate of 40% was seen in patients with liver metastases and a 63.2% response rate was observed in patients with soft tissue disease.

Two-phase III comparative studies, involving a total of 326 metastatic breast cancer patients who had failed on alkylating agents and 392 patients who had failed on anthracycline therapy, have been performed with docetaxel at the recommended dose and regimen of 100 mg/m² every 3 weeks.

In patients who had failed on alkylating agents, docetaxel was compared to doxorubicin (75 mg/m² every 3 weeks). Without affecting overall survival time (docetaxel 15 months vs. doxorubicin 14 months) or time to progression (docetaxel 27 weeks vs. doxorubicin 23 weeks), docetaxel increased response rate (52% vs. 37%, p=0.01) and shortened time to response (12 weeks vs. 23 weeks, p=0.007). Three docetaxel patients (2%) discontinued the treatment due to fluid retention, whereas 15 doxorubicin patients (9%) discontinued due to cardiac toxicity (three cases of fatal congestive heart failure). This study supported the indication for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.

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

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

The application for broadening the indication to patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) is based on the results of one phase III study of docetaxel vs vinorelbine/ifosfamide in patients previously treated for NSCLC and two phase III studies against best supportive care, one in previously treated patients and the other in naive patients. The study vs vinorelbine/ifosfamide failed to show a significant effect on the primary endpoint (overall survival), while it showed a significant increase in one secondary endpoint, the response rate, which was 10.5% and 6.5% in the docetaxel 100 and 75 mg/m² respectively compared with 0.8% in the vinorelbine/ifosfamide. The study versus best supportive care in previously treated patients was analysed in two parts corresponding to two successive periods and doses of docetaxel: 100 and 75 mg/m². In this study a significant increase in overall survival (p = 0.016) was observed only in the second period. Docetaxel treatment showed also positive effects in several secondary endpoints of this study: Time to progression was significantly improved in the overall docetaxel group (10.6 weeks versus 6.7 weeks), as well as in docetaxel 75 mg/m² (12.3 weeks versus 7.0 weeks) and in docetaxel 100 mg/m² subgroups (9.1 weeks versus 5.9 weeks). Docetaxel treatment was also associated with a clinical benefit translating in reduced need for analgesics, symptomatic agents and radiotherapy. The lower dose was generally better tolerated than the higher dose. Taken together the data from this study lead to a positive benefit/risk ratio of docetaxel 75 mg/m² in second line treatment of locally advanced or metastatic NSCLC.

A significant benefit in overall survival versus best supportive care (p = 0.026) was obtained also in the third phase III study conducted in chemotherapy-naive patients. The response rate was in the range, which is known to be achieved with the most active single agents. Furthermore, less patients treated with docetaxel needed complementary radiotherapy or pharmacotherapy compared with

patients receiving only best supportive care. This trial demonstrates a positive benefit/risk ratio for docetaxel 100 mg/m² over best supportive care in chemotherapy-naïve NSCLC patients. However, it was considered by the CPMP that combination chemotherapy containing cisplatin is the currently best treatment in that setting. Therefore, a comparison vs such an active comparator should be provided to consider an extension of the indication to first-line treatment.

First-line treatment of locally advanced or metastatic breast cancer in combination with doxorubicin

One large phase III study, involving 429 previously untreated patients with metastatic disease, has been performed with doxorubicin (50 mg/m²) in combination with docetaxel (75 mg/m²) (AT) versus doxorubicin (60 mg/m²) in combination with cyclophosphamide (600 mg/m²) (AC). Both regimens were administered on day 1 every 3 weeks. The patient population was representative of metastatic breast cancer patients commonly referred for first-line treatment and there were no imbalance in the patient characteristics between the two arms. The primary efficacy parameter was time to progression (TTP) using a logrank test to compare the two treatment groups. The secondary efficacy parameters were response rate, duration of response, survival, quality of life and although not defined in the protocol the time to treatment failure was also analysed.

TTP provided by a strict TTP analysis (accounting for a list of conventions in case of missing tumor assessments) was significantly longer in the AT arm versus AC arm, p=0.045. The median TTP was 35.1 weeks (95%CI : 32.7 ; 37.6) in AT arm and 31.4 weeks (95%CI : 27.4 ; 34.3) in AC arm. The classic analysis of TTP (taking into account the real date of documented progression independently of the missing tumor assessments), lead to a larger difference regarding the median TTP between the two groups (p=0.0138) being 37.3 weeks (95% CI: 33.4 - 42.1) in the AT arm and 31.9 weeks in the AC (95% CI: 27.4 - 36.0) arm. Overall response rate (ORR) was significantly higher in the AT arm versus AC arm, p=0.009. The ORR was 59.3% (95%CI : 52.8 - 65.9) in AT arm versus 46.5% (95%CI : 39.8 - 53.2) in AC arm. The median duration of response was longer in the AT group compared to the AC group (45.7 weeks vs 39.0 weeks in ITT, p=0.3125). This difference was however not statistically significant. Distribution of time to treatment failure was statistically different between the two treatment groups (p=0.0479). The median time to failure was 25.6 weeks on AT (95% C.I.: 22.3 - 28.0) and 23.7 weeks on AC (95% C.I.: 20.6 - 26.0). There was no difference regarding quality of life between the two treatment arms. Furthermore the overall survival was similar in the two groups (20.4 months on AT and 20.9 months on AC), but the study was not considered mature enough to detect any clinically relevant difference between treatment groups due to the fact that 57% of the patients were still alive at the cut-off date. Moreover, the majority of the censored observations (76% in AT and 81% in AC) are distributed before or in the vicinity of the observed median in each group (i.e. before 21 months). The second or the third line of treatment usually drives the survival in metastatic disease. The proportion of patients who received further chemotherapy was balanced in the two arms (47% of patients in AT arm and 48% of patients in AC arm). However more patients in AC arm received further chemotherapy with Taxanes (27% of patients in AC arm vs 6% in AT arm) and more patients in AC arm received docetaxel as further therapy than in AT arm (18.1% vs 2.3%). Taking into consideration that docetaxel is the only cytotoxic agent to have shown in large randomized phase III trials a statistically significant increase of survival in metastatic breast cancer patients who previously failed an anthracycline containing regimen, the fact that 18.1% of the AC group received docetaxel as second-line treatment may have had a positive impact on their overall survival.

Overall the study demonstrated the superiority of the docetaxel-doxorubicin combination over the cyclophosphamide-doxorubicin combination in terms of TTP and response rate.

First line treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer.

One main phase III study (TAX 326), one supportive phase III (TAX 308) and a series of uncontrolled phase I and phase II platinum-based combination studies were submitted to support this indication. The recommended dose for docetaxel was identified as 75mg/m², for the combination with cisplatin. Three of the studies assessed clinical pharmacokinetics and confirmed an absence of a pharmacokinetic interaction between docetaxel and the platins.

The application was based on a single 3-arm randomised controlled trial (TAX 326) comparing two drug combinations of docetaxel plus cisplatin or carboplatin with the “standard” active drug regimen of vinorelbine plus cisplatin in chemotherapy-naïve patients with NSCLC.

Selection criteria for TAX 326 include patients of age ≥ 18 years, with unresectable locally advanced and/or recurrent (Stage IIIB) or metastatic (Stage IV), histologically or cytologically confirmed NSCLC, and at least one measurable or evaluable lesion. Recurrence was defined as evident tumour progression after surgical or radiation treatment. Previous therapies were limited to surgery for NSCLC, and/or radiation therapy for NSCLC. No prior treatments with a biologic response modifier or chemotherapeutic agents were allowed. A Karnofsky Performance Status >70 was required, as well as adequate organ function. Patients with symptomatic brain or leptomeningeal metastases, or history of brain or leptomeningeal metastases unless adequately treated (stable for 4 weeks after completion of that treatment), untreated superior vena cava syndrome, untreated spinal cord compression, hypercalcemia of malignancy, clinically significant (\geq Grade 3 NCI criteria) pericardial effusion, or asymptomatic (i.e. requiring thoracentesis) pleural effusion, were excluded.

Patients were randomised to one of the following treatment arms:

- ARM A: docetaxel 75 mg/m² + cisplatin 75mg/m² day 1 q21 days
- ARM B: docetaxel 75 mg/m² + carboplatin AUC6 day 1 q21 days
- ARM C: vinorelbine 25 mg/m² days 1, 8, 15, and 22; + cisplatin 100 mg/m² day 1 q28 days

The primary efficacy endpoint was overall survival. The secondary efficacy endpoints were: Overall objective Tumor Response, Time to Progression, Safety, and QOL, Other clinical benefit parameters. The main efficacy results are summarized in the table 1:

	Docetaxel+Cisplatin versus Vinorelbine+cisplatin		Docetaxel+Carboplatin versus Vinorelbine+Cisplatin	
	Docetaxel +Cisplatin n=408	Vinorelbine +cisplatin n=404	Docetaxel +Carboplatin n=406	Vinorelbine +cisplatin n=404
Overall Survival	p=0.044		p=0.66	
Adjusted Log-rank Test				
Median Survival (months)	11.3	10.1	9.4	9.9
95% CI	[10.1, 12.4]	[9.2, 11.3]	[8.7, 10.6]	[9.0, 11.3]
1-year Survival (%)	46	41	38	40
95 % CI	[42,51]	[36,46]	[33,43]	[35,45]
Median Time to Progression (weeks)	22.0	23.0	20.0	22.0
95% CI	[21, 25]	[21, 27]	[19.0, 23.0]	[19.0, 25.0]
Adjusted Log-rank test	p= 0.617		p= 0.235	
Overall Response Rate (%)	31.6	24.5	23.9	24.5
95% CI	[27.1, 36.4]	[20.4, 29.0]	[19.8, 28.3]	[20.4, 29.0]
Fischer's Exact Test	p=0.029		p=0.870	
Change in Global QoL:				
LCSS	p= 0.064		p= 0.016	
EQ5D	p= 0.016		p <0.001	
Change in Karnofsky PS	p= 0.028		p <0.001	
Weight loss $\geq 10\%$	p < 0.001		p <0.001	
Change in pain score (LCSS)	p = 0.033		p= 0.355	

LCSS: lung cancer symptom scale; EQ5D:European Quality of Life scale, 5-Dimensions

In combination with capecitabine for locally advanced or metastatic breast cancer.

The claim was mainly based on comparative data deriving from a large randomised controlled clinical trial (SO14999). This claim was supported by an additional and independent interaction trial (SO15304) investigating PK interactions between docetaxel and capecitabine in a population of patients with advanced solid tumours in general. **Study SO14999** is an open-label, multicenter, multinational, randomised, parallel-group phase III clinical trial. It was designed to compare the efficacy and safety profile of capecitabine (intermittent schedule) in combination with ("reduced") docetaxel vs. ("full dose") docetaxel administered as single agent in patients with locally advanced or

metastatic breast cancer failing an anthracycline-containing (first-line) regimen. Stratification was done by previous paclitaxel treatment since paclitaxel pre-treatment, or failure, was not an exclusion criteria.

- **Combination arm:** Capecitabine orally at 1250 mg/m² twice daily (within 30 minutes after completing a meal) for two weeks followed by a one week rest. Docetaxel as a 1-hour infusion of 75 mg/m² on the first day of each cycle (every 3 weeks) together with appropriate co-medication (prophylaxis of hypersensitivity reactions by oral corticosteroid).
- **Docetaxel single agent arm:** Docetaxel as a 1 hour infusion of 100 mg/m² on the first day of each cycle (every 3 weeks) together with appropriate co-medication (prophylaxis of hypersensitivity reactions by oral corticosteroid).

The primary endpoint was time to progression (TTP).

The Secondary endpoints were: Survival, Objective Response (OR), Quality of Life (EORTC QLQ-30 (version 2.0) form and its breast cancer module QLQ-BR23).

In a subgroup of 16 patients of the combination arm, the PK parameters c_{max} , t_{max} , AUC_{∞} and $t_{1/2}$ (apparent half life) were determined on study day 14 and 77. Blood samples, overall not exceeding 90 ml, were drawn pre-dose (capecitabine), and at 0.5, 1, 2, 3, 4, 5, 7, and 10 hours after administration of capecitabine at aliquots of 5 ml.

Two different populations were analysed for TTP; the ITT and per protocol population and two different analysis (primary and on treatment approach) of these populations were planned. The efficacy results from Study SO14999 are presented in tables 2 and 3.

Assessment/Approach	docetaxel+capecitabine		Log-rank p-value	Hazard Ratio
All Randomized Patients				
“Primary” Approach			0.0001	0.643
Number of Events	230	247		
Median	186 days	128 days		
95% CI	[165, 198]	[105, 136]		
Standard Population				
“Primary” Approach			0.0001	0.632
Number of Events	182	212		
Median	179 days	127 days		
95% CI	[163, 195]	[97, 136]		
All Randomized Patients				
“On Treatment” Approach			0.0001	0.608
Number of Events	120	157		
Median	188 days	128 days		
95% CI	[164, 209]	[105, 136]		
Standard Population				
“On Treatment” Approach			0.0002	0.620
Number of Events	112	139		
Median	180 days	127 days		
95% CI	[152, 205]	[97, 136]		

Table 3: Summary of Survival Results

Assessment/Approach	Combination Therapy	Monotherapy	Log-rank p-value	Hazard Ratio	Result of Statistical Analysis (Combination versus Monotherapy)
All Randomized Population					
• Time to Death			0.0126	0.775	Combination therapy

Number of Events	183	201			superior
Median	442	352			
95% CI	[375,497]	[298,387]			

The objective of this trial to show statistically significant superiority in terms of the primary endpoint time to progression has been reached (186 vs. 128 days). This obviously also translates in a relevant prolongation (90 days; 442 vs. 352 days) of overall survival (Table 3). The overall pattern of significant and similar results clearly indicates that the combination results in more objective tumour responses, which translate in prolonged TTP and OS.

Further details can be found in the EPAR of Xeloda (capecitabine).

In combination with trastuzumab in HER2+ metastatic breast cancer

This indication was mainly based on data from Study M77001, which is discussed below. Supportive data were provided from Study JP16003, a clinical pharmacology study in Japanese patients, assessing the pharmacokinetics of trastuzumab and Taxotere in combination and Publications from six completed and two ongoing phase II supportive efficacy studies. Safety information from four ongoing multicenter trials on HER2-positive MBC patients treated with the combination of trastuzumab and Taxotere was provided.

Study M77001 was an open-label, comparative, multicenter, multinational, randomized phase II study, conducted as pivotal trial. Eligible patients had to have metastatic breast cancer (MBC) with HER2 overexpression/amplification (IHC3+ and/or FISH positive) who had not previously received chemotherapy for advanced disease. All patients were randomised to receive trastuzumab in combination with docetaxel or docetaxel alone.

The primary endpoint was overall response rate (ORR) in each treatment arm (complete response CR plus partial response PR) during the treatment period. Secondary endpoints were to characterise the safety profile of docetaxel plus Trastuzumab and of docetaxel as a single agent in patients with HER2-positive MBC, to determine the time to progression (TTP), progression-free survival (PFS), time to treatment failure (TTF), time to response, duration of response and overall survival. Results in the full analysis set are presented below.

Table 4: Overall tumour response and best tumour response

	Docetaxel alone (n=94)	Docetaxel plus Trastuzumab (n=92)	Difference in response rate
Responders	34 (36.2%)	56 (60.9%)	24.7%
Complete response	2 (2.1%)	6 (6.5%)	(10.2%,39.2%)
Partial response	32 (34.0%)	50 (54.3%)	p=0.001
Non-responders	60 (63.8%)	36 (39.1%)	
Stable disease	39 (41.5%)	25 (27.2%)	
Progressive disease	14 (14.9%)	11 (12.0%)	
Missing (response not assessed)	7 (7.4%)	0 (0.0%)	

Table 5. Time related secondary endpoints (months, median and range) at 6 months after last recruitment

	Docetaxel alone (N=94)	Docetaxel plus Trastuzumab (N=92)

Time to response	n=41	n=64
Duration of response	2 (1.1-3.8)	1.6 (0.8-7.2)
	4.2 (1.2-10.7)	8.3 (1.6-27.4)
Number with PD	57 (60.6%)	57 (62%)
Number without PD (censored)	37 (39.4%)	35 (38%)
Time to progression (TTP) p=0.0001	6.1 (0.2-12.2)	10.6 (0.5-29)
Number dying	34 (36.2%)	20 (21.7%)
Number surviving (censored)	60 (63.8%)	72 (78.3%)
Overall survival (OS) p=0.0002	18.3 (0.2-27)	27.7 (1.5-29.7)
Number progressing or dying	58 (61.7%)	58 (63%)
Number surviving and disease free (censored)	36 (38.3%)	34 (37%)
Progression free survival (PFS) p=0.0001	6.1 (0.2-12.2)	10.6 (0.5-29)
Number with failure	79 (84%)	68 (73.9%)
	15 (16%)	24 (26.1%)
Number without failure	3.7 (0-9.2)	9.2 (0.2-24.4)
Time to treatment failure (TTF) p=0.0001		

n denotes the number of patients reaching the endpoint, N the total number of patients in the specified treatment group and population

Table 6. Efficacy outcomes in Anthracycline pre-treated and Anthracycline naïve subgroups

	Anthracycline pre-treated patients			Anthracycline naïve patients		
	Docetaxel alone n=52	Docetaxel + Trastuzumab n=59	p-value	Docetaxel alone n=42	Docetaxel + Trastuzumab n=33	p-value
ORR IRR* (95%CI)	35% (22-49%)	58% (44-70%)	0.015	38% (24-54%)	67% (48-82%)	0.014
Median (range) duration of response (months)	4.2 (1.2-6.9)	8.8 (1.7-21.9)		4.6 (1.9-10.7)	8.2 (1.6-27.4)	
Median (range) TTP (months)	5.4 (0.2-11.4)	10.6 (0.5-23.3)	0.0001	6.9 (0.7-12.2)	10.4 (7.6-29)	0.0113
Median (range) survival (months)	21.9 (0.2-27)	25 (4.5-29.7)	0.0198	18.3 (1.3-21.8)	** (1.5-29)	0.0028

* response as assessed by independent radiological review reconciled with investigators assessment (eg where overriding clinical information available)

**= median could not be estimated due to extensive censoring

The MAH was required to update the 6-months analysis of the M77001 study to include data up to 12 months after the last patient entered.

Table 7 Efficacy Data from the M77001 Study – 12 month Analysis (ITT)

	Docetaxel alone n=94	Docetaxel plus Trastuzumab n=92	p-value
ORR IRR*	34% (CR/PR 2/30)	61% (CR/PR 6/50)	0.0002
ORR investigator	44% (CR/PR 5/36)	70% (CR/PR 12/52)	0.001
Median (range) duration of response (months)	5.1 (1.2 – 32.1+)	11.4 (1.6 – 34.4+)	0.0011
Median (range) TTP (months)	5.7 (0.2 – 33.6+)	10.6 (0.5 – 36+)	0.0001
Median (range) survival (months)	22.1 (0.2 – 36.2+)	30.5 (5.9 –36+)	0.0062

*Response as assessed by independent radiological review reconciled with investigator assessment (eg where overriding clinical information available)

+ censored observations

The presented results from the pivotal study M77001, demonstrate that a significantly higher overall tumour response was observed in the patients receiving the combination docetaxel + Trastuzumab compared to the monotherapy group with docetaxel. The combination Trastuzumab + docetaxel is more effective than docetaxel alone for anthracycline pre-treated (administered in adjuvant intent) and anthracycline naïve patients in terms of overall response rate, median duration of response, median

TTP and median survival in patients with HER2-positive metastatic breast cancer. Supportive efficacy data for the combination therapy are available from 6 completed and 2 ongoing studies reported in the literature.

The estimated median survival times have increased with longer follow up to an estimated median of 30.5 months compared with the docetaxel alone arm (estimated median 22.1 months) (p=0.0062).

It was considered that although single agent docetaxel is not an approved first line treatment in metastatic breast cancer, it is widely used. Moreover as use of anthracyclines in the adjuvant setting is current practice, metastatic patients are usually unsuitable to be treated with anthracyclines. As efficacy was proven both in anthracycline-naïve and anthracycline-pre-treated patients, there are no grounds to restrict the indication to patients who have had prior anthracycline therapy or for whom anthracycline therapy is not suitable.

In conclusion 3-weekly Taxotere in combination with Herceptin administered weekly is an efficacious treatment of patients with HER2-positive metastatic breast cancer. In principal no new emerging safety signals could be identified. The benefit risk ratio for Taxotere in the indication: in combination with trastuzumab for the treatment of those patients who have not received chemotherapy for their metastatic disease is therefore positive.

Further details can be found in the EPAR for Herceptin (trastuzumab)

Adjuvant treatment of early breast cancer in combination with doxorubicin and cyclophosphamide

The main study, TAX316, is a prospective, parallel, non-blinded, randomized, positive-controlled, multinational phase III trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes.

Both regimens were to be administered for a total of 6 cycles unless treatment was precluded by relapse, subject refusal, or unacceptable toxicities.

TAC: Doxorubicin was administered first at 50 mg/m², by 15-minute iv infusion followed by Cyclophosphamide 500 mg/m², by 1-to 5-minute iv infusion and in one-hour interval between the end of doxorubicin infusion, Taxotere, 75 mg/m², by 1-hour intravenous infusion, every 3 weeks.

FAC: Doxorubicin was administered first at 50 mg/m², by 15-minute intravenous infusion followed by 5-fluorouracil, at 500 mg/m², by 15-minute intravenous infusion and Cyclophosphamide 500 mg/m², by 1-to 5-minute intravenous infusion, every 3 weeks.

G-CSF was used in case of febrile neutropenia or infection, for delayed recovery of neutrophil count at day 21 and as prophylactic treatment after a prior episode of febrile neutropenia. For both arms no primary prophylactic administration of G-CSF was permitted. Prophylactic antibiotic therapy was mandatory for all patients in the TAC group whereas patients in the FAC group received prophylactic antibiotics only after an episode of febrile neutropenia.

The primary objective was to compare disease-free survival (DFS). Overall survival (OS) is the main secondary objective and is defined as the time interval between the date of randomization and the date of death. Other secondary criteria are comparison of the two treatment groups quality of life (as measured by EORTC QLQ-C30 and the QLQ-BR23) and on the pathologic and molecular markers for predicting efficacy (P-glycoprotein, p53, Bcl-2, Bax, Bcl-X, Bag-1, hormone receptors and proliferation index). The results of the second interim analysis at 399 DFS events and at a median follow-up of 55 months, formed the basis of the approval. The majority of events were breast cancer relapses (85.5 %), second primary malignancies (11.5 %) and deaths (3 %).

Primary efficacy endpoint:

Table 8– Disease-Free Survival Per Axillary Lymph Nodes In All Randomized Subjects				
- By Randomization Group - ITT Analysis				
Number of positive				
nodes	Statistics	TAC	FAC	Log Rank test

All	N	745	746	
	Events (%)	172 (23%)	227 (30%)	
	3-year DFS	84%	76%	Stratified p=0.001
	5-year DFS	75%	68%	(two-sided)
	Hazard Ratio	0.72		
	95% CI	[0.59 - 0.88]		
1-3 Nodes	N	467	459	
	Events (%)	76 (16%)	114 (25%)	
	3-year DFS	90%	81%	One-sided p=0.00045
	5-year DFS	82%	74%	(Two-sided p=0.0009)
	Hazard Ratio	0.61		
	95% CI	[0.46 - 0.82]		
≥ 4 Nodes	N	278	287	
	Events (%)	96 (35%)	113 (39%)	
	3-year DFS	73%	67%	One-sided p=0.083
	5-year DFS	64%	58%	(Two-sided p=0.1663)
	Hazard Ratio	0.83		
	95% CI	[0.63 - 1.08]		
				p=0.1457
Treatment by nodal status interaction	Ratio of HR	1.34 [0.90 – 2.00]		
	Adjusted for covariates	1.27 [0.86 – 1.90]		p=0.2352

Secondary efficacy endpoints

Table 9– Overall Survival Per Axillary Lymph Nodes In All Randomized Subjects - By Randomization Group - ITT Analysis

Number of positive nodes				
	Statistics	TAC	FAC	Log Rank test
	N	745	746	
	Deaths (%)	91 (12%)	130 (17%)	
	3-year OS	92%	89%	Stratified p=0.008
All	5-year OS	87%	81%	(Two-sided)
	Hazard Ratio	0.70		
	95% CI	[0.53 - 0.91]		
	N	467	459	
	Events (%)	30 (6%)	63 (14%)	
	3-year OS	96%	91%	Two-sided p=0.0002
1-3 Nodes	5-year OS	94%	86%	
	Hazard Ratio	0.45		
	95% CI	[0.29 - 0.70]		
	N	278	287	
	Events (%)	61 (22%)	67 (23%)	
	3-year OS	86%	85%	Two-sided p=0.7224
≥ 4 Nodes	5-year OS	77%	73%	
	Hazard Ratio	0.94		
	95% CI	[0.66 - 1.33]		
Treatment by nodal status interaction	Ratio of HR	2.05 [1.18 – 3.58]		p=0.0112
	Adjusted for covariates	1.85 [1.06 – 3.24]		p=0.0301

Clinical efficacy results of study TAX316 for the entire study population are convincing in terms of decrease of the risk of disease relapse and survival benefit. The results are clinically relevant and reached statistical significance: DFS (HR 0.72, 95% CI 0.59 – 0.88, p=0.001); OS (HR 0.70, 95% CI

0.53 – 0.91, p=0.008). The robustness of this substantial benefit was confirmed using a multivariate Cox model adjusted for prognostic covariates.

The results are particularly relevant in the 1-3 nodes stratum. For the 4 or more positive nodes stratum, the results although numerically higher for the TAC arm did not reach statistical significance. The final analysis of TAX316 which the MAH committed to conduct (expected in 2007) will answer the question whether there is a significant benefit of TAC for both strata separately.

It is well established that nodal involvement is an important prognostic or risk factor for subjects with operable breast cancer, and that, irrespective of the treatment; DFS and OS decrease as the number of positive lymph nodes increases. With regard to the primary endpoint, DFS, the 95% confidence interval for subjects with 4+ is clearly overlapping the confidence interval for the subjects with 1-3 nodes (0.46-0.82 in nodes 1-3 compared to 0.63-1.08 in 4+). Regarding OS, this overlapping is less marked but it exists (0.29-0.70 in nodes 1-3 compared to 0.66-1.33 in 4+). It seems that with this interim analysis the benefit-risk-ratio is not fully defined for patients in the stratum N 4+. This will be possible after the final analysis. This issue is addressed within the SPC.

The final analysis of the study TAX 316 planned after observing a total of 590 DFS events, will be submitted (late 2007), as well as an annual safety update based on a yearly data review by the existing independent data monitoring committee for study TAX 316.

In combination with prednisone or prednisolone in hormone refractory metastatic prostate cancer (HRPC).

The indication was obtained from the results from the multicenter phase III randomized trial TAX 327. The study compared Taxotere administered either every three weeks or weekly in combination with prednisone versus mitoxantrone in combination with prednisone in the treatment metastatic hormone-refractory prostate cancer. Study participants were subjects with histologically / cytologically metastatic adenocarcinoma of the prostate unresponsive or refractory to hormone therapy (based on castration by orchiectomy and/or LHRH agonists with or without antiandrogens or estramustine.)

Treatment regimen:

Arm A (MTZ q3w, reference arm): Mitoxantrone 12 mg/m² intravenously every 21 days, plus prednisone 10 mg orally given daily, for 10 cycles. Prednisone could be continued after completion of 10 cycles.

Arm B (TXT q3w, experimental arm): Docetaxel 75 mg/m² intravenously (day 1) every 21 days, plus prednisone 10 mg orally given daily, for 10 cycles.

Prophylactic dexamethasone 8 mg per os was to be administered at 12 hours, 3 hours and 1 hour before Taxotere infusion.

Arm C (TXT qw, experimental arm): Docetaxel 30 mg/m² intravenously on days 1, 8, 15, 22, 29, every 6 weeks, plus prednisone 10 mg orally given daily, for 5 cycles.

Dexamethasone 8 mg per os was to be administered 1 hour before docetaxel infusion.

In each study arm prednisone could be continued after completion of treatment.

The primary endpoint was overall survival. Secondary objectives were predefined reductions in pain, an improvement in QoL, a reduction of serum PSA levels of at least 50%, and objective tumor responses (the original time to progression (TTP) secondary endpoint was changed to event (pain, PSA, tumour, disease) progression free survival by *Amendment No.2*). Pain reduction (incidence and duration), prostate specific antigen (PSA) response (incidence and duration), response in patients with measurable disease, Quality of Life (using the Functional Assessment of Cancer Therapy –Prostate – FACT-P Questionnaire consisting of different subscales), safety, PK in combination with prednisone.

A total of 1006 subjects were randomized: 335 subjects in the TXT q3w group, 334 subjects in the TXT q1w group, and 337 subjects in the MTZ q3w group.

Efficacy Results

Table 10: Primary Efficacy Variable – Overall Survival, ITT Population:

	Combined TXT Groups	TXT q3w	TXT q1w	MTZ q3w
	N(%)	N(%)	N(%)	N(%)
Number of subjects in ITT population	669(100)	335(100)	334(100)	337(100)
Number of deaths	356(53.2)	166(49.6)	190(56.9)	201(59.6)
Number censored	313(46.8)	169(50.4)	144(43.1)	136(40.4)
Reason for censoring:				
- Dead after cutoff	6(0.9)	4(1.2)	2(0.6)	4(1.2)
- Death not observed	307(45.9)	165(49.3)	142(42.5)	132(39.2)
Death not observed	307(100)	165(100)	142(100)	132(100)
- Confirmed still alive*	302(98.4)	163(98.8)	139(97.9)	130(98.5)
KM median survival (mo)	18.27	18.92	17.38	16.49
<i>95% Confidence Interval</i>	<i>17.02 – 19.25</i>	<i>17.02 – 21.22</i>	<i>15.70 – 19.02</i>	<i>14.42 – 18.56</i>
KM survival probability at (%):				
12 mo	70.9	73.3	68.6	64.8
24 mo	33.5	37.2	29.9	28.5

Treatment Group Comparisons – Stratified Logrank Test**			
	Combined TXT Groups vs. MTZ q3w	TXT q3w vs. MTZ q3w	TXT qw vs. MTZ q3w
P value	0.0398	0.0094	0.3624
Nominal significance level	0.0400	0.0175	0.0175
Statistically significant	YES	YES	NO
Hazard ratio for overall survival***	0.834	0.761	0.912
<i>95% Confidence Interval</i>	<i>0.701 – 0.992</i>	<i>0.619 – 0.936</i>	<i>0.747 – 1.113</i>

* Relative to the survival cutoff date

** Stratified on baseline pain and baseline KPS as specified at randomisation.

*** From Cox proportional hazards model stratified by baseline pain and baseline KPS as specified at randomisation; for X versus Y, a hazard ratio < 1 favours X.

With regard to the primary endpoint of overall survival, combined Taxotere groups and Taxotere q3w treatment were statistically superior to mitoxantrone plus prednisone (HR=0.834 [0.701-0.992], p=0.0398; Taxotere q3w HR=0.761 [0.619-0.936], p=0.0094), while the difference was not statistically significant in the qw treatment arm (HR =0.912, [0.747-1.113, p=0.3624). Given the fact that Taxotere qw presented a better safety profile than TAX q3w, and that some patients may benefit from the qw schedule, this information is reflected in section 5.1 of the SPC.

A reduction in pain was more frequent among subjects receiving docetaxel every 3 weeks than among those treated with mitoxantrone, pain reduction rate of 34.6% vs 21.7% (p=0.01) respectively. No significant difference could be shown in the duration of pain response.

Rates of PSA response were significantly higher in subjects receiving docetaxel (45.4% vs 47.9% respectively) than those receiving mitoxantrone (31.7%), p=<0.001 for both comparisons. No significant difference was seen in the duration of PSA response.

Tumor response rates were numerically higher in both TXT groups (12.1% for TXTq3w, 8.2 % for TXTqw) as compared to the MTZ group (6.6 %), but the differences did not achieve statistical significance.

The QoL evaluated by fact-P, showed that the percentage of subjects who had improvement in the QoL was similar in subjects receiving docetaxel (22% for the every 3 weeks and 23% for the weekly) and significantly higher compared to those subjects treated with mitoxantrone (13%), p=0.009 and p=0.005 respectively.

Safety

Locally advanced or metastatic breast cancer after failure of prior chemotherapy

The safety profile of docetaxel has been extensively studied. The most important adverse events are severe neutropenia and infections and fluid retention. Most of the adverse events described below were reported in the initial trials and confirmed in trials performed and reported after granting of the Marketing Authorisation. Rare events, revealed in these post-authorisation trials, are described accordingly and have been added to the appropriate sections of the SPC. Treatment was discontinued because of side effects in 10-15% of patients.

Leuconeutropenia: frequent short lasting at the recommended dose, readily reversible, non-cumulative and not complicated by fever and infections (22%). However, when a mucositis exists (longer/repeated infusion, simultaneous use of corticosteroids), it could lead to an increased risk of neutropenic fever and infections.

Fluid retention: although not severe in most cases, some patients discontinue the treatment; the final report from a study investigating the pathophysiology of fluid retention in 24 advanced breast and ovary cancer patients treated with docetaxel at the recommended dosage confirmed the relationship between the cumulative dose of docetaxel and the development of a reversible fluid retention syndrome. In general the most frequent clinical appearance of fluid retention was a peripheral soft pitting oedema of the lower extremities moving to a hard lymphedema at a later stage. The mechanism in the generation of the fluid retention involved two steps: progressive congestion of the interstitial space by proteins and subsequently by water between the 2nd and 4th cycle followed by a later insufficiency in the lymphatic drainage. Premedication with corticosteroids allows for significant reduction in its incidence and severity. The original recommendation for fluid retention premedication was 5-day regimen with an oral corticosteroid. The Marketing Authorisation Holder provided a report on 3-day versus 5-day corticosteroids regimen. Following the assessment of the report it was concluded that the recommended premedication to reduce both the incidence and severity of fluid retention could be shortened to a 3-day steroid regimen.

Acute hypersensitivity reactions: they encompass a broad spectrum of clinical manifestations but appear to be of limited severity. Their mechanism is unclear and the use of antihistaminic agents (anti H1 or anti H2) has not been effective in reducing them.

Myalgias and arthralgias: the mechanism is also unclear, and no preventive measures have been specifically studied.

Neuro-sensory toxicity was observed in about 50% of patients, mostly grade I.

Skin toxicity, mostly grade 1 (erythema), had been observed in 64% of the patients at the time of the marketing authorisation. In addition, localised bullous eruptions were rarely reported in the fifth Periodic Safety Assessment Report (PSUR). To reflect these findings, the sections 4.4 “Special warnings and special precautions for use” and 4.8 “Undesirable effects” of the SPC and the package leaflet have been revised accordingly.

Mucositis occurred in 43% of patients, with some dependence upon the schedule regimen proposed.

Hepatic and renal toxicity: increases in serum transaminases (AST, ALT), bilirubin and alkaline phosphatase greater than 2.5 times the upper limit of normal (ULN) were observed in less than 5% of the patients. Due to eligibility criteria the initial studies, provided limited data in patients with abnormal liver function tests at baseline. In subsequent studies it was observed that the occurrence of serious adverse events was increased in patients with liver impairment at baseline ($p < 0.01$). To reflect these findings, the sections 4.4 “Special warnings and special precautions for use” and 4.8 “Undesirable effects” of the SPC have been revised accordingly. Grade I increase in creatinine (1.26-2.5×N) was reported for 11.1% of patients for an overall incidence of 13.2%.

Other: Other events usually mild to moderate in severity included alopecia, asthenia, stomatitis, neurosensory and gastro-intestinal symptoms and their incidence appeared to be stable. In the overall population only asthenia had an incidence of severe toxicity greater than 10%. The results of a monocentric open label non-randomised study carried out on 98 patients showed that the usage of cold

cap, commonly used with other antimetabolic agents, can be useful in preventing alopecia induced by docetaxel therapy. Based on the assessment of PSURs the following adverse events have been added to section the SPC: gastrointestinal perforations, neutropenic enterocolitis, myocardial infarction and thromboembolic events.

After the Marketing Authorisation had been granted on 27 November 1995, during Phase II and III clinical trials, some hospital pharmacists misinterpreted the instructions for preparation of Taxotere infusion solution. Consequently, new information related to the content of vials, clarification on the preparation of the infusion solution and reference to aseptic preparation were introduced into the sections 6.5 "Nature and contents of container" and 6.6 "Instructions for use/handling" of the SPC. The Labelling and Package Leaflet were amended accordingly.

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

Adverse effects in all studies were in line with those observed in patients with breast cancer. Generally a higher incidence of grade 3-4 adverse events, especially infections and pulmonary adverse events, were observed in NSCLC patients treated with 100 mg/m² compared with the 75 mg/m² dose level.

First-line treatment of locally advanced or metastatic breast cancer in combination with doxorubicin

Adverse events were reported using the NCI-CTC scale and COSTART. The doxorubicin /docetaxel (AT arm) showed a higher incidence of severe neutropenia (90% versus 68.6%), febrile neutropenia (33.3% versus 10%), Grade 3-4 infection (8% versus 2.4%), Grade 3-4 diarrhea (7.5% versus 1.4%), severe asthenia (8.5% versus 2.4%), and severe pain (2.8% versus 0%) than the doxorubicin/cyclophosphamide (AC) arm. On the other hand, AC arm showed a higher incidence of severe anaemia (15.8% versus 8.5%) than AT arm, and, in addition, a higher incidence of severe cardiac toxicity: congestive heart failure (3.8% versus 2.8%), absolute LVEF decrease $\geq 20\%$ (13.1 % versus 6.1%), absolute LVEF decrease $\geq 30\%$ (6.2% versus 1.1%). Overall the combination doxorubicin/docetaxel seems to be less well tolerated than the AC combination. However, this toxicity appears to be predictable and manageable, as indicated by the discontinuation rates, which were similar in the two treatment arms and the quality of life, which was comparable and stable during treatment and follow-up in both arms. Moreover, toxic deaths occurred only in 1 patient in the AT arm (congestive heart failure) and in 4 patients in the AC arm (1 due to septic shock and 3 due to congestive heart failure).

First line treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer.

In general, the investigational treatment docetaxel plus cisplatin and the control treatment V+Cis showed a comparable safety profile. The treatment duration was comparable for both groups despite the higher number of treatment discontinuations due to adverse events in the V+Cis treatment group.

When the safety profile of the combination D75+Cis is compared to the known safety profile of approved indications (docetaxel monotherapy and docetaxel in combination with doxorubicin) no unlabelled undesirable effects are apparent. In general, the incidence of undesirable effects was in the range of that found with docetaxel monotherapy at the dose of 75 mg/m² or with docetaxel in combination with doxorubicin (DA). The incidence of neurotoxicity of D75+Cis is in the range reported for docetaxel monotherapy at a dose of 100 mg/m². Higher incidences were reported only for vomiting (D75+Cis: 53.4 %, DA: 45 %) and anorexia (D75+Cis 28.8 %, D75 single agent: 19 %).

Adjuvant treatment of early breast cancer in combination with doxorubicin/ cyclophosphamide

The safety profile of docetaxel associated with AC is as expected. However in the adjuvant treatment of early breast cancer severe, serious and long-term toxicity is of even more interest than in other applications. In comparison with the control arm, TAC safety profile is worse and raises serious concerns in terms of hematotoxicity, cardiotoxicity, colitis, and leukaemia.

Approximately one third of patients experience severe AEs and serious AEs. More than 8 % of patients show serious and severe AEs related to study treatment. This is mainly due to the incidences of neutropenia, febrile neutropenia and fever in the absence of infection, which are clearly more frequent during TAC treatment. Consequently the use of G-CSF and antibiotics was much higher in the TAC group. Prophylactic antibiotics were compulsory for TAC treatment. Approximately 30 % of

patients received G-CSF as curative or prophylactic treatment in the TAC group compared to 5.6 % in the FAC group. In spite of this prophylaxis there were twice as much neutropenic infections in the TAC group. Six percent of the patients withdrew from the trial due to adverse events.

Generally the pattern of the reported AEs is as expected for the combination with doxorubicin. There were clearly more AEs of fluid retention, anemia (including transfusion requirements, myalgia, stomatitis, neuro-sensory, taste perversion, thrombocytopenia and arthralgia in the TAC group compared to the control. Vomiting was observed more often in the FAC group.

Overall the toxicity is considerably high but it is manageable with prophylactic antibiotics and often G-CSF and close monitoring of the patients during the treatment phase. Appropriate information and precautions have been included in the SPC.

With respect to long-term toxicity the profile of TAC is also unfavourable compared to FAC: Alopecia remains in 3.2 % of TAC patients (vs. 1.4 % FAC), more TAC-treated patients stay with ongoing neuro-sensory toxicity (TAC: n = 9, FAC n=2), peripheral edema (TAC: n = 18, FAC n=3) than FAC-treated patients. Cardiac failure was observed in 12 TAC patients and 4 FAC patients. So far 3 patients in the TAC group and 1 in the FAC group developed acute leukemia.

The occurrence of secondary leukaemia is a well known toxicity of anthracyclines. This adverse effect is under review for docetaxel. The possibility of an increased risk with the association of docetaxel and doxorubicin cannot be disregarded.

Furthermore, the SPC section 4.4 is amended in order to give appropriate information regarding the management of acute toxicity (neutropenia, gastrointestinal toxicity) and description of late toxicity (cardiotoxicity, leukaemia). Since some toxicities remain a concern in an adjuvant setting, an intensive monitoring concerning cardiotoxicity, secondary leukaemia, and serious gastrointestinal toxicity (including colitis, perforation, and hemorrhagic diarrhea) is ongoing.

In combination with capecitabine for locally advanced or metastatic breast cancer

For the investigation of safety, all clinical adverse events encountered during the study, as well as abnormal laboratory test values and results of regular physical examinations (vital signs) had to be clearly recorded in the CRF. All adverse events (AEs) and abnormal laboratory parameters were assessed according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC) grading system.

The safety of the combination of capecitabine plus (“reduced”) docetaxel vs. “full dose” docetaxel can be briefly summarised as follows: Overall, the results are consistent with the predictions of the safety profile of the single substances. In general, the combination is more toxic than docetaxel monotherapy. The difference is mainly due to “hand-foot syndrome” (HFS) and to a lesser extent also due to gastrointestinal symptoms, namely diarrhoea and stomatitis. The physician can handle the AEs by dose modifications without affecting efficacy in the combination arm.

Age of more than 60 years represents a risk factor for treatment related grade 3 – 4 AEs, serious AEs and withdrawals from treatment. Based on the results of this subgroup analysis, a starting dose reduction of capecitabine to 75% (950 mg/m² twice daily) is recommended for patients 60 years of age or more treated with the combination of capecitabine plus docetaxel and if no toxicity is observed the dose of capecitabine may be cautiously escalated to 1250 mg/m² twice daily.

Safety in Her2+ metastatic breast cancer in combination with trastuzumab

The data set for the safety evaluation was based on the pivotal study M77001 and on the Japanese clinical pharmacology study JP16003. Additional information is provided from 2 interim safety reports and from published literature reports. Approximately 700 patients with HER2-positive MBC exposed to Trastuzumab plus docetaxel have been treated. However, the database with fully assessable safety information is limited and consists mainly of the data from the pivotal study.

Patients always received Trastuzumab in the recommended dose, however the dosing regimen of docetaxel varied across studies. Overall, the treatment was well tolerated with no new or unexpected safety signals.

The incidence of common, non-serious adverse events was higher in the combination with trastuzumab, as was the incidence of severe (grade 3 or 4) and serious adverse events.

The addition of Trastuzumab to Taxotere increased the incidence of transient grade 3/4 neutropenia (32% versus 22% in the Taxotere alone arm). The same was observed for febrile neutropenia (23% versus 17%), suggesting that Trastuzumab may exacerbate the Taxotere-associated myelosuppression. No new concerns have been identified regarding the severity and frequency of infusion-related reactions with the combination Trastuzumab+ Taxotere. However, the risk of neutropenic events is increased and exceeds that of Taxotere alone.

There were fewer safety related withdrawals for patients in the combination arm.

The safety profile described in the main analysis (6 months after last patient entered) has not changed with the addition of data up to the 12 month cut-off. No new unexpected adverse events have occurred and the relative incidence of different types of AEs is similar to that seen at the 6-month analysis.

The incidence of decreases in LVEF (falls $\geq 15\%$ or absolute value $<40\%$) remains the same.

It can be concluded that no new emerging safety concerns could be identified and in principle, the toxicity profile is consistent with that of the two drugs alone.

Safety in Hormone refractory prostate cancer patients

The indication „prostate cancer“ differs from others licensed in the respect that the patients are elderly men, who are more likely to suffer from infra- and supravescical obstruction and resulting renal impairment. Patients with renal impairment (elevated creatinine) have not been included in the submitted clinical trial.

The most common adverse events are alopecia, nail changes, anorexia, myalgia, arthralgia, fatigue, and tearing. In principle no new emerging safety signals were identified. Among the most commonly reported and possibly severe adverse events of docetaxel are anaemia, neutropenia, sensory and motor neuropathy, and gastro-intestinal symptoms.

More severe and serious (grade 3-4) adverse events were observed in the Taxotere groups (45.8 % and 43.0 %) than in the mitoxantrone group (34.6%). Laboratory safety data also indicated a higher toxicity of Taxotere as compared with mitoxantrone (anaemia, grade 3-4 neutropenia, febrile neutropenia, and neutropenic infections). Neurotoxicity and gastrointestinal toxicity was more common in the Taxotere groups, whereas mitoxantrone exhibited more cardiotoxicity, resulting in decreased left ventricular function. However the rate of cardiotoxicity in the Taxotere groups is not negligible, particularly in this aged population.

Otherwise, the safety profile of Taxotere is modified in the oldest treated population (>75), as follows : increased rate of fatigue, infection, gastrointestinal toxicities, peripheral oedema, sensory neuropathy, nail change and anorexia. This severity and seriousness of fluid retention in older patients, including an analysis of risk factors, is detailed in the section 4.4 of the SmPC.

5. Overall conclusions and benefit/risk assessment

The CPMP recommended in 1995 that the Marketing Authorisation should be granted under exceptional circumstances, as information from comparative randomised Phase III clinical studies was not yet available at that time. In 1997, two Phase III randomised comparative trials in anthracycline or alkylating agents resistant patients were submitted by the Marketing Authorisation Holder and confirmed the favourable benefit/risk profile of Taxotere. Since all specific obligations stated in Annex II C of the CPMP Opinion dated 19 December 1996 have been fulfilled and the benefit/risk profile has been reassessed, there were no remaining grounds for the Marketing Authorisation to be kept under exceptional circumstances. The Marketing Authorisation has been amended accordingly.

The CPMP Members have, during the review process of the initial and subsequent applications, agreed that there are sufficient clinical data to support clinical safety and efficacy allowing a positive recommendation for granting the Marketing Authorisation for Taxotere for the following indications:

Breast cancer

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

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

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

TAXOTERE (docetaxel) in combination with trastuzumab is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.

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

Non-small cell lung cancer

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

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

Prostate cancer

TAXOTERE (docetaxel) in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

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