London, 20 April 2005
Product name: **PAXENE**
Procedure No. **EMEA/H/C/399/II/26**

SCIENTIFIC DISCUSSION

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Additional indication:

Treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy.

As Taxol is also approved in the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy, clinical data related to this indication can be extrapolated to support the same indication for Paxene (see also 6.2, 6.3.1 and 7.1).

Introduction

In advanced NSCLC (stage III or IV) with best supportive care alone, the median survival of patients is no greater than 3-6 months and 1-year survival less than 10%. In the early 1990's it was shown that cisplatin-based chemotherapy improved survival by a median of 2 months; symptoms in stage III/IV disease were relieved in up to three-quarters of patients, and QoL was better than with best supportive care alone (Belani & Langer 2002). The introduction of further cytotoxic agents, e.g. taxanes (such as paclitaxel), gemcitabine, vinorelbine, carboplatin, during the 1990s presented new options for single-agent and combination therapy leading to the standard platinum (cisplatin or carboplatin)/paclitaxel treatment regimen (Belani & Langer 2002, Crinò & Calandri 2002).

Efficacy of paclitaxel (Taxol)/cisplatin combination as first-line chemotherapy in advanced NSCLC was demonstrated in two Bristol-Myers Squibb randomised, controlled trials in more than 900 patients with locally advanced or metastatic NSCLC (CA139-103, Giaccone et al. 1998) and CA139-165, Bonomi et al. 2000).

Clinical efficacy in the pivotal trials

In study CA139-103, 332 patients with locally advanced or metastatic NSCLC were randomised to receive cisplatin (80 mg/m^2) on day 1 in combination with teniposide (100 mg/m^2) on days 1, 3, and 5 (n=166), or cisplatin (80 mg/m^2) and paclitaxel (175 mg/m^2 over 3 h) on day 1 (n=166) every 3 weeks fora maximum of 6 cycles. There was no statistically significant difference increase in duration of survival with cisplatin/paclitaxel vs cisplatin/tenoposide (9.5 vs. 9.9 months or progression free survival (5.1 vs. 5.0 months for cisplatin/teniposide. There was a significant benefit in terms of overall response rate (37% cisplatin/paclitaxel vs. 26% cisplatin/teniposide. Overall, although a survival advantage could not be demonstrated with cisplatin/paclitaxel compared to cisplatin/teniposide in this trial, the higher response rates, lesser side effects and improved QoL were considered important results in a palliative population.

In the second study CA139-165, 599 patients with stage IIIB or IV disease were randomised to receive cisplatin (75 mg/m^2 on day 1) and etoposide (100 mg/m^2) on days 1, 2 and 3 (n=200), or cisplatin (75 mg/m^2) and a low dose of paclitaxel (135 mg/m^2 over 24 h, n=198), or cisplatin (75 mg/m^2) and a high dose of paclitaxel (250 mg/m^2 over 24 h) with G CSF (n=201) every 3 weeks. Although median survival only approached significance in each individual paclitaxel-containing arm (p=0.097 and 0.090 for high dose paclitaxel/cisplatin/G-CSF and low-dose paclitaxel/cisplatin, respectively) compared to etoposide/cisplatin (due to better than anticipated survival in the etoposide/cisplatin arm), survival in the combined paclitaxel arms was significantly longer than with etoposide/cisplatin (9.7 months versus 7.4 months; 1-year survival 38% versus 32% [p=0.049]). Notably, survival in the subgroup with stage IIIB disease (19% of the overall trial population) was substantially greater in the combined paclitaxel/cisplatin arms compared to etoposide/cisplatin (13.1 months versus 7.9 months [p=0.152]).

With respect to progression free survival greater benefits were noted in favour of the paclitaxel-containing arms and highly statistically significant results were noted for the high dose and combined paclitaxel arms compared to etoposide/cisplatin ($p \leq 0.007$ for both comparisons). Finally response rates also strongly favoured the paclitaxel-containing arms 13%, 30% and 26% for the etoposide/cisplatin, high dose paclitaxel/cisplatin/G-CSF ($p<0.001$ versus etoposide/cisplatin) and low-dose paclitaxel/cisplatin regimens (p=0.003 versus etoposide/cisplatin), respectively. No differences in outcomes were noted for the high and low-dose paclitaxel treatment arms in comparison to one another.

In conjunction these two pivotal phase III studies are the primary basis for the existing Taxol indication for the treatment of advanced NSCLC, and provide the principal data for the current application. However, prolongation of survival with paclitaxel/cisplatin is modest and further improvement in therapy is likely to require integration of novel, molecularly targeted agents such as epidermal growth factor receptor inhibitors (e.g. gefitinib) in combination with cytotoxic chemotherapy (Belani & Langer 2002, Crinò & Calandri 2002) or improvement of the dosage schedules. Some of these questions have been addressed in the 12 clinical trials published since the pivotal BMS studies.

Literature Review

Results from 12 studies (11 phase III studies and 1 large phase II), on the efficacy and safety of paclitaxel-containing combination treatment, mainly paclitaxel/platinum combinations, in patients with advanced NSCLC are summarised and discussed (Section 2.7.3 NSCLC). These studies provided additional evidence for the efficacy of paclitaxel/cisplatin in patients with advanced NSCLC.

Patient population and study designs

Data from more than 6,000 eligible patients (4,300 patients treated with paclitaxel-containing regimens and 1,700 patients with other chemotherapeutic regimens) with stage III or, the majority, stage IV NSCLC from these mainly open, randomised, multicenter studies are summarised in Table 8.1. All patients were between 18 and 87 years old. Prior surgery or radiotherapy was allowed but had to be completed approximately 2 4 weeks before study entry. Probably all patients were chemotherapy-naïve (no detailed information given in the study of Gatzemeier et al. 2000). The majority of the patients presented with a performance status of 0-1 (ECOG or WHO performance status), or Karnofsky index of 90-80%.

The overall objectives of these trials were to compare survival, time to disease progression, response to treatment, and QoL of paclitaxel-containing regimens vs. other chemotherapeutic regimens.

Paclitaxel was combined with cisplatin, carboplatin, or gemcitabine, respectively; furthermore a triplet regimen of Paclitaxel cisplatin gemcitabine. Patients received 125 mg/m^2 (over 1 h), 175 - 225 mg/m^2 (over 3 h) or 135 mg/m^2 (over 24 h) paclitaxel in combined schedules. The mean number of cycles ranged from 2 - 6, some patients received up to 10 cycles; in the majority of studies the regimens were administered in 3-week intervals (Table 8.1).

Table 1: Overview of paclitaxel combination trials on efficacy and safety in NSCLC patients

Reference	Eligible patients (n)	Dosage (test) Interval (weeks) /n of cycles	Dosage (control) Interval (weeks) / n of cycles
Belani et al. 2003	401	PTX LD/CAR LD (n=132): PTX 100 mg/m^2 + CAR AUC 2* weekly for 3 of 4 w 4 w / 4 cycles PTX HD/CAR LD (n=134): PTX 150 mg/m^2 cycle 1, 100 mg/m^2 cycle 2 + CAR AUC 2* weekly for 6 of 8 w 8 w / 2 cycles	PTX LD/CAR HD (n=135): PTX 100 mg/m^2 weekly for 3 of 4 w + CAR AUC 6*, d 1 of each 4 w cycle 4 w / 4 cycles
Comella et al. 2001	354	PTX/CIS/GEM (n=114 treated): PTX 125 mg/m^2, 1 h + CIS 50 mg/m^2 + GEM 1,000 mg/m^2, d 1 + 8 3 w / 3-5 cycles	CIS/GEM (n=112 treated): CIS 100 mg/m^2 d 1 + GEM 1,000 mg/m^2 d 1 + 8 + 15 4 w, 2-5 cycles CIS/GEM/VIN (n=117 treated): CIS 50 mg/m^2 d 1, + GEM 1,000 mg/m^2 + VIN 25 mg/m^2, d 1 + 8 3 w, 3-5 cycles

Reference	Eligible patients (n)	Dosage (test) Interval (weeks) /n of cycles	Dosage (control) Interval (weeks) / n of cycles
Gatzemeier et al. 2000	414	PTX/CIS (n=207): PTX 175 mg/m^2, 3 h + CIS 80 mg/m^2 3 w, 5 cycles	CIS HD (n=207): CIS 100 mg/m^2 3 w, 3 cycles
Glorieux et al. 2001	130	PTX HD/CAR (n=99): PTX 200 mg/m^2, 3 h + CAR AUC 6* 3 w, 4 cycles	PTX LD/CAR (n=31): PTX 175 mg/m^2, 3 h + CAR AUC 6 3 w, 4 cycles
Herbst et al. 2004	1,037	PTX/CAR/GEF HD (n=347): PTX 225 mg/m^2, 3 h, d 1 + CAR AUC 6*, d 1 + GEF p.o. 500 mg/d 3 w, 5 cycles PTX/CAR/GEF LD (n=345): PTX 225 mg/m^2, 3 h, d 1 + CAR AUC 6*, d 1 + GEF p.o. 250 mg/d 3 w, 5 cycles	PTX/CAR/PL (n=345): PTX 225 mg/m^2, 3 h, d 1 + CAR AUC 6*, d 1, + PL p.o. 3 w, 6 cycles
Kelly et al. 2001 (QoL: Moinpour et al. 2002)	408	PTX/CAR (n=206): PTX 225 mg/m^2, 3 h + CAR AUC 6*, d 1 3 w, 4 cycles	CIS/VIN (n=202): CIS 100 mg/m^2 +VIN 25 mg/m^2/w, d 1 3 w, 3 cycles
Kosmidis et al. 1997	49	PTX HD/CAR (n=20): PTX 225 mg/m^2, 3 h + CAR AUC 6* 3 w, 2-6+ cycles	PTX LD/CAR (n=29): PTX 175 mg/m^2, 3 h + CAR AUC 6* 3 w, 2-6+ cycles
Kosmidis et al. 2002	479	PTX/GEM (n=238): PTX 200 mg/m^2, 3 h, d 1 + GEM 1,000 mg/m^2, d 1 + 8 3 w, up to 6 cycles	PTX/CAR (n=241): PTX 200 mg/m^2, 3 h, d 1 + CAR AUC 6*, d 1 3 w, up to 6 cycles
Rosell et al. 2002	608	PTX/CAR (n=306): PTX 200 mg/m^2, 3 h, d 1 + CAR AUC 6* 3 w, 4 cycles	PTX/CIS (n=302): PTX 200 mg/m^2, 3 h, d 1, + CIS 80 mg/m^2 3 w, 4 cycles
Scagliotti et al. 2002	607	PTX/CAR (n=201): PTX 225 mg/m^2, 3 h, d 1 + CAR AUC 6*, d 1 3 w, up to 8 cycles	CIS/GEM (n=205): CIS 75 mg/m^2, d 2 + GEM 1,250 mg/m^2, d 1 + 8 3 w, up to 8 cycles CIS/VIN (n=201): CIS 100 mg/m^2, d 1 + VIN 25 mg/m^2, d 1 + 8 + 15 + 22 (after w 12: VIN weekly) 4 w, up to 8 cycles
Schiller et al. 2002	1,155	PTX/CAR (n=290): PTX 225 mg/m^2, over 3 hours, d 1, + CAR AUC 6*, d 1 3 w, n.d. on number of cycles CIS/GEM (n=288): CIS100 mg/m^2 d 1 + Gem 1,000 mg/m^2, d 1 + 8 + 15 4 w, n.d. on number of cycles CIS/DOC (n=289): CIS 75 mg/m^2, d 1 + DOC 5 mg/m^2, d 1 3 w, n.d. on number of cycles	PTX/CIS (n=288): PTX 135 mg/m^2, over 24 hours, d 1, + CIS 75 mg/m^2, d 2 3 w, n.d. on number of cycles

Reference	Eligible patients (n)	Dosage (test) Interval (weeks) /n of cycles	Dosage (control) Interval (weeks) / n of cycles
Smit et al. 2003	480	PTX/GEM (n=161): PTX 175 mg/m^2, over 3 hours, d 1, + GEM 1,250 mg/m^2, d 1 + 8 3 w, median 4 cycles CIS/GEM (n=160): CIS 80 mg/m^2, d 1 + GEM 1,250 mg/m^2, d 1 + 8 3 w, median 5 cycles	PTX/CIS (n=159): PTX 175 mg/m^2, over 3 hours, d 1 + CIS 80 mg/m^2, d 1 3 weeks, median 5 cycles

* mg/ml/min, PTX, CIS and CAR are administered intravenously (i.v.). AUC: area under the curve, CAR: carboplatin, CIS: cisplatin, d: day, DOC: docetaxel, GEF: gefitinib, GEM: gemcitabine, HD: high dose, LD: low dose, min: minute, n.d.: no data, PL: placebo, p.o.: per oral, PTX: paclitaxel, VIN: vinorelbine

Efficacy results

The clinical response (overall response), survival (overall survival, 1- and 2-year survival), time to disease progression/progression-free survival, and QoL of cisplatin- and carboplatin-based paclitaxel-containing regimens are compared with each other and with other chemotherapeutic regimens, respectively.

Clinical Response

Final data on overall response rates were reported in 11/12 studies. Overall response rates with paclitaxel/cisplatin ranged from 21-32%. These results are consistent with those observed in the pivotal BMS studies (overall response rates 25%- 41% in B-MS CA139-103, and CA139-165, respectively). No further significant differences with regard to response were noticed between paclitaxel/cisplatin (various dosage regimens) and other chemotherapeutic regimens tested, i.e. paclitaxel/carboplatin (Rosell et al. 2002, Schiller et al. 2002), paclitaxel/gemcitabine (Smit et al. 2003), cisplatin/gemcitabine (Smit et al. 2003, Schiller et al. 2003) and cisplatin/docetaxel (Schiller et al. 2003).

Overall response rates during paclitaxel/carboplatin therapy ranged from 17- 32%. There was no significant difference in overall response between paclitaxel/carboplatin (various dosage regimens), paclitaxel/cisplatin (Rosell et al. 2002, Schiller et al. 2002, see above), and other chemotherapeutic regimens, i.e. paclitaxel/gemcitabine (Kosmidis et al. 2002), cisplatin plus docetaxel (Schiller et al. 2002), cisplatin plus gemcitabine (Scagliotti et al. 2002, Schiller et al. 2002), cisplatin plus vinorelbine (Kelly et al. 2001), and paclitaxel/carboplatin/gefitinib (Herbst et al. 2004).

In one study, overall response rates between different doses of paclitaxel (175 mg/m^2 and 200 mg/m^2 over 3 hours, respectively) combined with fixed doses of carboplatin (AUC 6) were compared. The overall response rates were comparable: 26% in the paclitaxel (low-dose) and 23% (high-dose) arm (Glorieux et al. 2001). Different weekly application schemes of paclitaxel/carboplatin showed similar efficacy with regard to response parameters. However, in comparison with a 25% historical control rate, a lower overall response with paclitaxel/cisplatin 150 mg/m^2 in cycle 1, 100 mg/m^2 in cycle 2/AUC 2 weekly was observed (p=0.04) (Belani et al. 2003).

Table 2: Clinical response to paclitaxel-containing regimens (pooled data)

Treatment arms[&a]	Response (%)					Reference(s)
Paclitaxel/cisplatin-containing regimens						
PTX/CIS: PTX 175–200, 3 h + CIS 80 3 w intervals	OR 26-32 OR: Sig diff between PTX/CIS vs CIS HD (26 vs 17%, p=0.028) described by Gatzemeier et al. (2000), n.s. diff to CIS/GEM, CIS/DOC, PTX/CAR, PTX/GEM, for details see Section 2.7.3 NSCLC	CR 0-2	PR 25-32	SD 34-52	PD 20-24	Gatzemeier et al. 2000 Rosell et al. 2002 Smit et al. 2003
or PTX 135, 24 h + CIS 75 3 w intervals	OR 21	CR <1	PR 21	SD 18	PD 49	Schiller et al. 2002
PTX/CIS/GEM: PTX 125, 1 h + CIS 50 + GEM 1,000 3 w intervals	OR 48 OR: PTX/CIS/GEM and CIS/GEM/VIN (44%) superior to CIS/GEM (28%, p<0.02), for details see Section 2.7.3 NSCLC	CR 4	PR 44			Comella et al. 2001
Paclitaxel/carboplatin-containing regimens						
PTX/CAR(/PL): PTX 175-225, 3 h + CAR AUC 6 3 w intervals	OR 17-32 OR: N.s. diff between diff dosages of PTX/CAR compared to PTX/CAR/GEF (30%), CIS/VIN (28%), CIS/GEM (22-30%), CIS/DOC (17%), PTX/GEM (35%), PTX/CIS (see above), for details see Section 2.7.3 NSCLC	CR 0.5-2	PR 21-31	SD 18-	PD 18-49	Glorieux et al. 2001* Herbst et al. 2004 Kelly et al. 2001 Kosmidis et al. 2002 Rosell et al. 2002* Scagliotti et al. 2002* Schiller et al. 2002
Paclitaxel weekly administration						
PTX LD/CAR LD: PTX 100 + CAR AUC 2 weekly 4 w intervals PTX HD/CAR LD: PTX 150/100 cycle 1/2 + CAR AUC 2 weekly 8 w intervals PTX LD/CAR HD PTX 100 weekly + CAR AUC 6 4 w intervals	OR: 18-32 PTX LD/CAR LD: 24 PTX HD/CAR LD: 18 PTX LD/CAR HD: 32 n.s. diff In comparison to a 25% historical control rate, PTX HD/CAR LD (18%) showed a sig diff (p=0.04)					Belani et al. 2003*

[&] all PTX, all CIS, all GEM doses: mg/m^2, [a] all CAR AUC: mg/ml/min, * Response = primary endpoint, CAR: carboplatin, CIS: cisplatin, CR: complete response, diff: difference, DOC: docetaxel, GEF: gefitinib, GEM: gemcitabine, HD: high dose, LD: low dose, mo: months(s), n.d.: no data available, n.s.: not significant, OR: overall response, PD: progressive disease, PL: placebo, PR: partial response, PTX: paclitaxel, SD: stable disease, TTP: time to disease progression, VIN: vinorelbine, w: week(s)

Survival

Data on overall survival were available from 11of the/12 published studies. Overall survival was the primary endpoint in 7 of these and the secondary endpoint in the remaining studies. OS ranged from 7.8- 9.8 months in patients who were treated with paclitaxel/cisplatin (various dosage regimens) compared to 9.7 and 9.9 months, in studies CA139-103 and CA139-16, respectively.

The efficacy of paclitaxel/cisplatin was not significantly different from high-dose cisplatin (Gatzemeier et al. 2000), paclitaxel/carboplatin (Rosell et al. 2002, Schiller et al. 2002) or other comparative chemotherapeutic treatments, i.e. paclitaxel plus gemcitabine (Smit et al. 2003), cisplatin

plus gemcitabine (Smit et al. 2003), or cisplatin plus docetaxel (Schiller et al. 2003). However, Rosell et al. (2002) noticed a significant difference in favour of paclitaxel/cisplatin in after 22 additional months follow-up: overall survival was 9.8 months in the paclitaxel/cisplatin arm vs.8.2 months in the paclitaxel/carboplatin arm (p=0.019). Addition of gemcitabine to paclitaxel/cisplatin resulted in significantly prolonged survival vs. cisplatin/gemcitabine alone (approx. 11.9 months vs. 8.9 months, p<0.05). In the same study another triple combination cisplatin/ gemcitabine/vinorelbine was also superior to cisplatin/gemcitabine (approx. 11.9 months p<0.05) (Comella et al 2001).

During treatment with various dosage regimens of paclitaxel/carboplatin OS ranged from approximately 7.4 to10.4 months. In a comparison of different doses of paclitaxel (175 mg/m^2 and 200 mg/m^2, each over 3 hours) combined with fixed doses of carboplatin (AUC 6) OS was not statistically significantly higher with high-dose paclitaxel (8.5 months vs. 7.4 months in the low-dose paclitaxel arm) (Glorieux et al. 2001). In a study of weekly paclitaxel comparing different dosage regimens of paclitaxel/carboplatin, OS survival ranged from about 7.2 to 11.4 months. The differences were not significant (Belani et al. 2003).

Data on 1- and/or 2-year survival were available from 8 studies (Table 3). One-year survival rates ranged from 30 - 38% in patients treated with paclitaxel/cisplatin; in addition, in one study 2-year survival rates were reported to be 10% with paclitaxel/cisplatin (Schiller et al. 2002). These data compare to 1-year survival rates of 39-43% reported in the pivotal BMS studies (CA139-103 and CA139-165), and a 2-year rate of 19% in study CA139-103 (2-year data not available for CA139-165). In patients receiving paclitaxel/carboplatin 1- and 2-year survival rates ranged from 33- 47%, and 11 - 19%, respectively. With weekly administration of paclitaxel in combination with carboplatin, the ranges for 1-year and 2-year survival rates of 31 - 47% and 10 - 19%, respectively, were similar (Belani et al. 2003, see Table 8.3).

Table 8.3 Effects of paclitaxel-containing regimens on overall survival and 1–and 2-year survival

Treatment arms[&a]	Overall survival (mo) (range)	1- and 2-year survival (range)	Significance / Comments	Reference(s)
Paclitaxel/cisplatin-containing regimens				
PTX/CIS: PTX 175–200, 3 h + CIS 80 PTX 135, 24 h + CIS 75 3 w intervals	8.1-9.8 7.8	30-38% and n.d. 31% and 10%	OS: n.s. diff to CIS HD (8.6 mo), CIS/GEM (8.1-8.9 mo), CIS/DOC (7.4 mo), PTX/GEM (6.7 mo), PTX/CAR (8.1-8.5 mo) 1- and 2-year survival: n.s. diff to CIS HD, CIS/GEM, CIS/DOC, PTX/CAR	Gatzemeier et al. 2000* Rosell et al. 2002 Smit et al. 2003* Schiller et al. 2002*
PTX/CIS/GEM: PTX 125, 1 h + CIS 50 + GEM 1,000 3 w intervals	≈11.9	n.d.	OS: PTX/CIS/GEM and CIS/GEM/VIN superior to CIS/GEM, p<0.05	Comella et al. 2001*

Treatment arms[&a]	Overall survival (mo) (range)	1- and 2-year survival (range)	Significance / Comments	Reference(s)
Paclitaxel/carboplatin-containing regimens				
PTX/CAR(/PL): PTX 175-225, 3 h + CAR AUC 6 3 w intervals	≈7.4-10.4	33-43% and 11-17%	OS: n.s. diff between different dosage regimens of PTX (LD/HD)/CAR (LD/HD) (≈7.2-11.4 mo). n.s. diff between PTX/CAR and CIS/VIN (8.6 mo), CIS/GEM (8.1-9.8 mo), CIS/DOC (7.4 mo), PTX/CIS (7.8-9.8 mo), PTX/GEM (9.8 mo), PTX/CAR/GEF HD (8.7 mo), PTX/CAR/GEF LD (9.8 mo) 1- and 2-year survival: n.s. diff to CIS/VIN, CIS/GEM, CIS/DOC, PTX/CIS, PTX/GEM, PTX/CAR/GEF HD, PTX/CAR/GEF LD	Glorieux et al. 2001 Herbst et al. 2004* Kelly et al. 2001* Kosmidis et al. 2002* Rosell et al. 2002[#] Scagliotti et al. 2002 Schiller et al. 2002
Paclitaxel weekly administration				
PTX LD/CAR LD: PTX 100 + CAR AUC 2 weekly 4 w intervals PTX HD/CAR LD: PTX 150/100 cycle 1/2 + CAR AUC 2 8 w intervals PTX LD/CAR HD: PTX 100 weekly + CAR AUC 6 4 w intervals	≈7.2-11.4	31-47% and 10-19%	OS: PTX LD/CAR LD: ≈7.2 PTX HD/CAR LD: ≈9.3 PTX LD/CAR HD: ≈11.4 mo n.s. diff 1-and 2 year survival: n.s. diff	Belani et al. 2003

* Survival = primary endpoint, [&] all PTX, all CIS, GEM doses: mg/m^2, [a] CAR AUC mg/ml/min, [#]sig diff between PTX/CAR and PTX/CIS in follow-up: 8.2 vs 9.8 mo, p=0.019. AUC: area under the curve, CAR: carboplatin, CIS: cisplatin, diff: difference, DOC: docetaxel, GEF: gefitinib, GEM: gemcitabine, HD: high dose, LD: low dose, n.d.: no data available, n.s.: not significant, OS: overall survival, PL: placebo, PTX: paclitaxel, VIN: vinorelbine, w: week(s)

Time to Disease Progression (TTP) or Progression-Free Survival (PFS)

Data on TTP or PFS was available from 112 studies. TTP was the primary endpoint in 1 study and secondary endpoint in the remaining studies reporting on this parameter.

PFS in patients treated with paclitaxel/cisplatin in the pivotal BMS studies (CA139-103 and CA139-165) ranged from 4.8-5.4 months. Reported TTP/PFS ranged from 3.4 to 4.2 months with paclitaxel/cisplatin (various dosages) in subsequent studies (Gatzemeier et al. 2000, Schiller et al. 2002). There was a significant difference in favour of paclitaxel/cisplatin reported vs high-dose

cisplatin (Gatzemeier et al. 2000), paclitaxel/gemcitabine (Smit et al. 2003), and paclitaxel/carboplatin (Rosell et al. 2002). However, cisplatin/gemcitabine was shown to be significantly superior to paclitaxel/cisplatin (Schiller et al. 2002). The addition of gemcitabine to paclitaxel/cisplatin an increased TTDP was reported which as significantly superior to cisplatin/gemcitabine (approx. 4.4 months, $p<0.02$) (Comella et al).

With paclitaxel/carboplatin TTP ranged from 3.1 to 7 months (Belani et al. 2003, Glorieux et al. 2001, Herbst et al. 2004 (paclitaxel/carboplatin/placebo), Kelly et al. 2001, Kosmidis et al. 2002, Scagliotti et al. 2002, Schiller et al. 2002). As above, Rosell et al reported longer TTP/PFS for paclitaxel/ cisplatin compared to paclitaxel/carboplatin (Rosell et al. 2002). However, no differences were noted between paclitaxel/carboplatin in various dose regimens and other chemotherapy regimens i.e. paclitaxel/ gemcitabine (Kosmidis et al 2002, cisplatin/docetaxel (Schiller et al 2002), cisplatin/gemcitabine (Scagliotti et al 2002, Schiller et al 2002), cisplatin/vinorelbine (Kelly et al 2001), and paclitaxel/carboplatin/gefitinib (Herbst et al 2004).

With weekly administration of paclitaxel, TTP ranged from approximately 4.9 to 7 months in patients receiving paclitaxel/carboplatin (Belani et al. 2003). The regimen of paclitaxel 100 mg/m^2 weekly plus carboplatin AUC 6 mg/ml/min (PTX LD/CAR HD, 4-week intervals) was superior to paclitaxel 100 mg/m^2 plus carboplatin AUC 2 mg/ml/min weekly (PTX LD/CAR LD, 4-week intervals).

In summary differences for TTP/PFS were noted between a number of regimens. With regard to the standard regimen of paclitaxel/cisplatin differences in TTP/PFS where observed favoured paclitaxel/cisplatin, except in comparison to cisplatin/gemcitabine. However, it should be noted that differences in TTP/PFS were not reflected in overall survival (see Table 8. 4).

Table 8.4 Effects of paclitaxel-containing treatment on time to disease progression (TTP) progression-free survival (PFS) (pooled data)

Treatment arms[&a]	TTP (mo) (range)	PFS (mo) (range)	Significant differences / Comments	Reference(s)
Paclitaxel/cisplatin-containing regimens				
PTX/CIS: PTX 175–200, 3 h + CI 80 PTX 135, 24 h + CIS 75 3 w intervals	4.1 3.4	4.2	TTP: PTX/CIS 4.1 vs CIS HD 2.7 mo, p=0.026 [1]; CIS/GEM 4.2 v s PTX/CIS 3.4 mo, p=0.001 [3] PFS: PTX/CIS 4.2 vs PTX/GEM 3.5 mo, p=0.044 [4] PTX/CIS 4.2 vs PTX/CAR 3 mo, p=0.035 [2]	Gatzemeier et al. 2000 [1] Rosell et al. 2002 [2] Schiller et al. 2002 [3] Smit et al. 2003 [4]
PTX/CIS/GEM: PTX 125, 1 h + CIS 50 + GEM 1,000 3 w intervals	≈6.8	--	TTP: PTX/CIS/GEM ≈6.8 vs CIS/GEM ≈4.4 mo, p<0.02	Comella et al. 2001
Paclitaxel/carboplatin-containing regimens				
PTX/CAR(/PL): PTX 175-225, 3 h + CAR AUC 6[a] 3 w intervals	3.1-6.3	3-4	TTP: n.s. diff between PTX/CAR(/PL) and PTX/CAR/GEF (HD/LD: 4.6 and 5.3 mo), PTX/GEM (6.1 mo), CIS/VIN (4 mo), CIS/GEM (4.2-5.3 mo), CIS/DOC (3.7 mo) PFS: PTX/CIS 4.2 mo vs PTX/CAR 3 mo, p=0.035 [2]	Glorieux et al. 2001 Herbst et al. 2004 Kelly et al. 2001 Kosmidis et al. 2002* Rosell et al. 2002 [2] Scagliotti et al. 2002 Schiller et al. 2002

Treatment arms[&a]	TTP (mo) (range)	PFS (mo) (range)	Significant differences / Comments	Reference(s)
Paclitaxel weekly administration				
PTX LD/CAR LD: PTX 100 + CAR AUC 2[a] weekly 4 w intervals PTX HD/CAR LD: PTX 150/100 cycle 1/2 + CAR AUC 2 weekly 8 w intervals PTX LD/CAR HD PTX 100 weekly + CAR AUC 6[a] 4 w intervals	≈4.9-7	--	TTP: PTX LD/CAR HD ≈7 mo PTX HD/CAR LD ≈24 mo PTX LD/CAR LD ≈4.9 mo, PTX LD/CAR HD vs PTX LD/CAR LD: p=0.01	Belani et al. 2003*

[&] all PTX, all CIS, GEM doses: mg/m^2, * Primary endpoint: time to disease progression, [a] mg/ml/min, CAR: carboplatin, CIS: cisplatin, diff: difference, DOC: docetaxel, GEF: gefitinib, GEM: gemcitabine, HD: high dose, LD: low dose, mo: months(s), n.d.: no data available, n.s.: not significant, PL: placebo, PFS: progression-free survival, PTX: paclitaxel, TTP: time to disease progression, VIN: vinorelbine

Quality of Life

In 5 of the analysed studies, the impact of paclitaxel/platinum-containing regimens on quality of life was evaluated. There were no significant differences for overall QoL.

Gatzemeier et al. 2000
A combination of paclitaxel plus low dose cisplatin was compared with high-dose cisplatin monotherapy in 414 patients with stage IIIB or IV NSCLC. There was no significant improvement in survival in the paclitaxel/cisplatin arm vs. the high-dose cisplatin arm; however, the combination produced a better clinical response, resulting in an increased time to progression.

Smit et al. 2003
Paclitaxel/cisplatin (control arm) was compared with paclitaxel/gemcitabine and cisplatin/gemcitabine in 480 patients with NSCLC. Cisplatin/gemcitabine and paclitaxel/gemcitabine did not increase overall survival vs. paclitaxel/cisplatin and there was shorter progression-free survival in the paclitaxel/gemcitabine group versus the paclitaxel/cisplatin group.

Comella et al. 2001
A cisplatin-containing triplet regimen of paclitaxel/cisplatin/gemcitabine (n=114 patients) was compared with cisplatin/gemcitabine (n=122) and a triplet of cisplatin/gemcitabine/vinorelbine (n=117) in 354 patients with NSCLC. The triplet regimens paclitaxel/cisplatin plus gemcitabine and cisplatin/gemcitabine/vinorelbine were associated with improved outcome

Rosell et al. 2002
A paclitaxel/carboplatin combination was compared with a paclitaxel/cisplatin combination in a total of 618 patients with stage IIIB or IV NSCLC. Paclitaxel/carboplatin yielded a similar response rate to paclitaxel/cisplatin; however, median survival was significantly longer with paclitaxel/cisplatin.

Discussion of Efficacy

In the pivotal BMS trials paclitaxel/cisplatin produced improvements in response (compared to teniposide/cisplatin and etoposide/cisplatin), survival and progression-free survival (compared to etoposide/cisplatin) in patients with advanced NSCLC. These data led to paclitaxel/cisplatin becoming the new reference regimen. Although survival benefits with paclitaxel/cisplatin in advanced are

modest, no other chemotherapeutic regimens have to date shown consistent survival or QOL advantages over paclitaxel/cisplatin.

Paclitaxel-containing chemotherapy regimens, mainly paclitaxel/cisplatin and paclitaxel/carboplatin, produced a favourable treatment response, an improvement in survival, time to disease progression and progression-free survival in patients with advanced NSCLC.

Paclitaxel/cisplatin was significantly superior to cisplatin monotherapy in terms of overall response and time to disease progression (Gatzemeier et al. 2000). In comparison with paclitaxel/carboplatin, paclitaxel/cisplatin showed comparable efficacy with regard to response, time to disease progression, and survival (overall survival, 1 and/or 2 year survival). In terms of progression-free survival/time to progression, paclitaxel/cisplatin was found to be superior to paclitaxel/carboplatin (Rosell et al. 2002), high-dose cisplatin (Gatzemeier et al. 2000) and paclitaxel/gemcitabine (Smit et al. 2003). However, TTP for paclitaxel/cisplatin was shorter than cisplatin/gemcitabine (Schiller et al 2002), although no difference in survival was noted.

Data from the pivotal BMS Taxol studies (CA139-103, and CA139-165) are supported by data from 4 subsequent studies. In each, paclitaxel/cisplatin combinations were administered and results consistent with those of the pivotal studies in terms of survival, progression free survival and response were observed. Only one study reported long-term results (Rosell et al. 2002). A survival update after 22 months additional follow-up yielded a median survival of 8.2 months (paclitaxel/carboplatin) and 9.8 months (paclitaxel/cisplatin) ($p=0.019$). These supplementary data therefore support the use of paclitaxel/cisplatin in the treatment of advanced NSCLC.

In conclusion, paclitaxel/cisplatin is established as first-line therapy of patients with advanced NSCLC. The recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3-week interval between courses. Paclitaxel/carboplatin is generally considered an alternative regimen with comparable activity. The place of alternative regimens (e.g. cisplatin/gemcitabine, paclitaxel/cisplatin/gemcitabine) in the therapy of advanced NSCLC is to be confirmed.

Clinical safety

Paclitaxel has been in clinical use for more than 10 years for treatment of patients with ovarian carcinoma, breast carcinoma, NSCLC and AIDS-related Kaposi's sarcoma. Its safety profile has remained consistent and is well known, being summarised in various standard manuals and review articles (Eisenhauer & Vermorken 1998, Dollery 1999, Fan 1999, Ginsberg et al. 1997, Sweetman 2002, Spencer & Faulds 1994, Sweetman 2002, Wiseman & Spencer 1998). The most common adverse events are neutropenia, anaemia, peripheral neuropathy, myalgia/arthralgia, mucositis, and alopecia (Wiseman & Spencer 1998). In addition, thrombocytopenia, infection, cardiovascular events, hepatic abnormalities (increases in bilirubin, alkaline phosphatase, aspartate aminotransferase) mild gastrointestinal effects, and hypersensitivity reactions have been reported (Eisenhauer & Vermorken 1998, Spencer & Faulds 1994).

<u>Taxol Data</u>

The following safety data were derived from the publications of the four pivotal BMS studies.

Ovarian cancer

The severity of neutropenia, febrile neuropenia, alopecia, and peripheral neurotoxicity was significantly greater ($p \leq 0.05$), in the paclitaxel/cisplatin group. Although neutropenia of grade 3 and 4 developed in the majority of women in the paclitaxel/cisplatin group, the incidence of febrile neutropenia was low and was consistent with the brevity of paclitaxel-induced myelosuppression. Peripheral neurotoxicity was more common in the paclitaxel group but overall was very mild.

As expected, substantially more patients in the paclitaxel/cisplatin group experienced severe myalgia, neurosensory and neuromotor symptoms, alopecia, and hypersensitivity reactions.

<u>NSCLC</u>

Haematologic toxicity (leukopenia, neutropenia, thrombocytopenia, anaemia) was significantly more frequent and more severe on cisplatin/teniposide than on paclitaxel/cisplatin. The more profound myelosuppression of cisplatin/teniposide led more frequently to febrile neutropenia and significantly more infectious episodes. More patients received blood transfusions on cisplatin/teniposide than on

paclitaxel/cisplatin. Cisplatin/teniposide also induced more stomatitis. On the other hand, more peripheral neurotoxicity, myalgia/arthralgia, and hypersensitivity reactions were observed on paclitaxel/cisplatin than on cisplatin/teniposide. Peripheral neurotoxicity on paclitaxel/cisplatin was more severe in patients who continued treatment with paclitaxel beyond six cycles. Two hypersensitivity reactions were observed on cisplatin/teniposide and 10 on paclitaxel/cisplatin. However, in only 3 cases on the paclitaxel/cisplatin arm were these severe requiring discontinuation of treatment.
Overall, treatment was discontinued because of toxicity in 3 patients on cisplatin/teniposide, and in 5 patients on paclitaxel/cisplatin. Cardiotoxicity and other non-haematologic side effects were similar in the two arms. Apart from alopecia, which was present in the majority of patients, and vomiting, which was severe in 12% of patients, overall, the other adverse events were infrequent.
There were 9 toxic deaths: 6 on cisplatin/teniposide (3.7%) and 3 on paclitaxel/cisplatin (1.9%). Six of these deaths were due to sepsis due to severe neutropenia, 5 of which occurred in the cisplatin/teniposide arm and 1 in paclitaxel/cisplatin arm. One patient on paclitaxel/cisplatin died of haemorrhage while severely thrombocytopenic after the third cycle, and another died of renal insufficiency. One patient on cisplatin/teniposide died of heart failure. In four additional patients, toxicity could not be definitely excluded as the cause of early death (3 patients in the cisplatin/teniposide arm: 2 possibly due to severe infection, 1 had a sudden cardiac death; 1 patient in the paclitaxel/cisplatin arm: sudden cardiac death) (Giaccone et al. 1998).

Literature Review

To provide an update to the safety data presented in the Taxol documentation, supportive safety data on paclitaxel-containing combinations from 20 additional studies published since 2000 (advanced ovarian cancer) and since 1997 (NSCLC), have been reviewed. These publications are identical with those analysed for efficacy, with the exception of Piccart et al. (2003), who did not report any safety data.
Overall, more than 12,000 patients with either advanced ovarian cancer (n=6,299) or advanced NSCLC (6,093), were eligible for safety analysis in the supportive clinical trials (see also Table 2.7.4-1). Of these, approximately 9,000 subjects were treated with paclitaxel-containing regimens (4,735 with ovarian cancer, 4,315 with NSCLC) and about 3,000 patients received other chemotherapeutic regimens (1,564 with ovarian cancer, 1,778 with NSCLC).

Adverse event profile of paclitaxel-containing combinations

Haematological and non-haematological adverse events reported in the analysed 20 clinical studies are summarised. Myelotoxicity, predominantly neutropenia or leukopenia, was most common and dose-limiting. Peripheral neuropathy occurred relatively frequently in patients treated with higher doses of paclitaxel and tended to be the main non-haematologic dose-limiting toxicity. Other adverse effects include myalgias and arthralgias, alopecia, diarrhoea and mucositis, which all appear to be dose-related, as well as some cardiac abnormalities (mainly asymptomatic bradycardia). Severe acute hypersensitivity reactions also occurred in some patients.

Significant differences in haematological and non-haematological toxicity) between the treatment regimens are presented in detail. Although direct comparisons between the various regimens tested are not possible since the dosages used in the different studies as well as the patient populations are heterogeneous, a comprehensive overview on the pattern of adverse events observed with paclitaxel-containing treatment regimens can be provided.

Haematological toxicity: Haematological adverse events were reported in both paclitaxel-containing and non-paclitaxel-containing regimens. In the majority of publications, severe (grade 3 and 4) toxicities were listed. The following haematologic toxicities occurred: neutropenia, leukopenia, thrombocytopenia, anaemia, febrile neutropenia/fever, (neutropenic) infections). Several patients required platelet or red blood cell transfusions due to thrombocytopenia or anaemia**.**
Neutropenia occurred significantly more frequently in patients receiving paclitaxel/cisplatin or paclitaxel monotherapy vs. patients were treated with single agent cisplatin (Muggia et al. 2000, and Gatzemeier et al. 2000, respectively) and tended to be more severe with paclitaxel monotherapy.
In two studies, neutropenia was more frequently noticed with paclitaxel/carboplatin than with paclitaxel/cisplatin (Du Bois et al. 2003b; Neijt et al. 2000); however, in other studies no significant

differences were found between both regimens (Ozols et al. 2003, Rosell et al. 2002, Schiller et al. 2002). Neutropenia was also reported to be significantly more frequent with cisplatin/vinorelbine vs. paclitaxel/carboplatin (Kelly et al 2001, Scagliotti et al 2002) or cisplatin/gemcitabine (Scagliotti et al 2002).

Anaemia: Anaemia was reported significantly more frequently, and with greater severity, among patients who were treated with paclitaxel/cisplatin or cisplatin monotherapy (Muggia et al. 2000) than paclitaxel monotherapy. It occurred more frequently with cisplatin/gemcitabine vs. paclitaxel/cisplatin (Schiller et al 2002, Smit et al 2003). Anemia occurred more frequently with cisplatin/vinorelbine vs. paclitaxel/carboplatin (Scagliotti et al 2002) however, Kelly et al (2001) noticed no significant difference with the same doses.

Febrile neutropenia and (neutropenic) infections: Febrile neutropenia was significantly more frequent with paclitaxel/cisplatin compared to paclitaxel/carboplatin or to cisplatin/gemcitabine in the study of Schiller et al. (2002); however, in another study no significant differences were found between paclitaxel/cisplatin and paclitaxel/carboplatin (Rosell et al. 2002).

Febrile neutropenia was seen more often in patients on paclitaxel/carboplatin/epirubicin vs paclitaxel/carboplatin; and was fatal in two patients on the triple arm (Kristensen et al. 2001). Fever occurred more frequently in patients on paclitaxel/cisplatin and high-dose paclitaxel single agent vs single agent cisplatin, and tended to be more severe with the high-dose paclitaxel regimen (Muggia et al. 2000).

Platelet and red blood cell transfusions: In the study of Smit et al. (2003) patients treated with cisplatin/gemcitabine needed transfusions significantly more often (95% red blood cell) than patients who received paclitaxel/cisplatin. In another study, packed red blood cell transfusions were significantly less on the paclitaxel/carboplatin arm vs cisplatin/gemcitabine and cisplatin/vinorelbine arms (Scagliotti et al. 2002). Du Bois et al. (2003b) described a higher frequency of red cell transfusions in patients receiving paclitaxel/carboplatin vs paclitaxel/cisplatin.

Non-haematological toxicity

Significant differences between the various treatment regimens are summarised below.

Neurotoxicity: Any grade of peripheral neuropathy was significantly more frequent with paclitaxel/cisplatin vs single agent cisplatin (Gatzemeier et al. 2000). Peripheral sensory neuropathy (all grades) occurred more frequently with paclitaxel/cisplatin vs paclitaxel/carboplatin (Du Bois et al. 2003b). However, several authors observed no significant differences in the frequency of neuropathy in paclitaxel/cisplatin and paclitaxel/carboplatin treated patients (Neijt et al. 2000, Rosell et al. 2002, Schiller et al 2000); however, Neijt et al did note that grade 1 neurotoxicity occurred earlier in patients who were treated with paclitaxel/cisplatin Neijt et al. 2000). Significant differences were found comparing two different doses of paclitaxel (175 mg/m^2 and 225 mg/m^2 over 3 h, respectively) in combination with carboplatin (AUC 6): neurotoxic events were more frequent with high-dose paclitaxel group (Bolis et al. 2004). Peripheral neuropathy (grade 3 and 4) was increased in the cisplatin/vinorelbine arm vs paclitaxel/carboplatin (Kelly et al. 2001). Mild neuropathy (grade 1-2) was significantly more common with the triplet regimens paclitaxel/cisplatin/gemcitabin and cisplatin/gemcitabine/vinorelbine vs cisplatin/gemcitabine (Comella et al. 2001).

Arthralgia/myalgia: Symptoms of arthralgia/myalgia were significantly more frequent with paclitaxel/cisplatin vs cisplatin monotherapy (Gatzemeier et al. 2000).

Gastrointestinal toxicity: Paclitaxel/carboplatin showed better tolerability than paclitaxel/cisplatin (Ozols et al. 2003). Nausea and vomiting were more often observed with paclitaxel/cisplatin than with paclitaxel/carboplatin (Du Bois et al. 2003b, Rosell et al. 2002, Schiller et al. 2000). Nausea and vomiting (grade 3 and 4) were increased with cisplatin/vinorelbine (Kelly et al. 2001, Scagliotti et al. 2002) and with paclitaxel/carboplatin/epirubicin (Kristensen et al. 2001) compared to paclitaxel/carboplatin. Furthermore, the frequency was higher with cisplatin/vinorelbine in comparison with cisplatin/gemcitabine (Scagliotti et al. 2002). However, with cisplatin/gemcitabine the frequency of grade 3 vomiting was approximately doubled in comparison to the triplet regimens

paclitaxel/cisplatin/gemcitabine and cisplatin/gemcitabine/vinorelbine In the triplet combinations the cisplatin dose was split between days 1 and 8 while in the doublet regimen the whole cisplatin dose was given on day 1 (Comella et al. 2001) which may have accounted for the difference in gastrointestinal tolerability. However, Smit et al. (2003) noticed no significant differences between cisplatin/gemcitabine, paclitaxel/cisplatin, or paclitaxel/gemcitabine for grade 3 and 4 nausea/ vomiting. In one study diarrhoea was more often noticed with paclitaxel/cisplatin than with paclitaxel/carboplatin (Rosell et al. 2002) but this was not the case in other studies.

Alopecia: Generally, with paclitaxel-containing regimens grade 1 and 2 alopecia was more frequently described than grade 3 to 4 alopecia. With paclitaxel monotherapy or paclitaxel/cisplatin, alopecia (grade 1 and 2) occurred significantly more frequently, and with greater severity, than in patients with single agent cisplatin (Muggia et al. 2000). Neijt et al. (2000) found no differences in alopecia, between paclitaxel/cisplatin and paclitaxel/carboplatin.

Nephrotoxicity: Renal toxicity was mainly grade 1 to 2. Grade 3 to 4 occurred at a significantly higher frequency with single agent cisplatin (100 mg/m^2) vs. paclitaxel/cisplatin (Muggia et al. 2000). Renal toxicity (all grades) was less frequent with paclitaxel/carboplatin vs. paclitaxel/cisplatin, rarely exceeding grade 1 or 2 (Du Bois et al. 2003b, Rosell et al. 2002). However, Neijt et al. (2000) found no differences in renal adverse events between paclitaxel/cisplatin and paclitaxel/carboplatin. Grade 3 to 5 renal toxicity was rare, being more frequent with cisplatin/gemcitabine vs. to paclitaxel/cisplatin (Schiller et al. 2000).

Mucositis: Mucositis was significantly more common with triple chemotherapy consisting of paclitaxel/carboplatin/epirubicin than paclitaxel/carboplatin (Kristensen et al. 2001).

Ototoxicity: Ototoxicity occurred mainly in platinum-containing combinations. Significantly more patients developed ototoxicity (any grade) with cisplatin monotherapy than with paclitaxel/cisplatin group (Gatzemeier et al. 2000). Ototoxicity was less frequent with paclitaxel/carboplatin vs paclitaxel/cisplatin and rarely exceeded grade 1 or 2 (Du Bois et al. 2003b).

Discontinuation from study and deaths

Discontinuation of therapy due to haematological or non-haematological adverse events, was reported for most studies.

There were 82 deaths due to therapy reported in the analysed studies. Cause of death included: haematological toxicity (grade 4 not further specified) with carboplatin followed by paclitaxel/ cisplatin and paclitaxel/cisplatin,), severe myelosuppression (paclitaxel/carboplatin), febrile neutropenia (paclitaxel/carboplatin/epirubicin), and non-haematological toxicity (grade 4 gastrointestinal toxicity (not further specified) with paclitaxel/cisplatin,, intestinal obstruction (paclitaxel/carboplatin/gefitinib HD), dehydration plus kidney failure (paclitaxel/carboplatin/gefitinib HD), pulmonary embolus (paclitaxel/carboplatin/gefitinib LD), cerebrovascular accident (paclitaxel/carboplatin/gefitinib HD), sepsis (paclitaxel/carboplatin/gefitinib LD, paclitaxel/ carboplatin), acute respiratory distress syndrome (paclitaxel/carboplatin), sudden death (paclitaxel/carboplatin/gefitinib HD), and rapidly progressive disease (paclitaxel/carboplatin).

Discussion of safety

In summary, myelosuppression (particularly neutropenia, leukopenia) was the most frequently reported haematological adverse event and occurred with all paclitaxel-containing regimens. Neuropathy (both sensory and motor), arthralgia/myalgia, asthenia, and alopecia (mainly grade 1 to 2) were the most frequently observed non-haematological adverse events with paclitaxel-containing regimens. Neurological toxicity occurred significantly more often with high-dose single agent cisplatin compared to high-dose single agent paclitaxel. Inconsistent results were obtained with paclitaxel/cisplatin versus cisplatin monotherapy: in one study paclitaxel/cisplatin was superior to cisplatin with regard to neurotoxicity while in another investigation cisplatin was superior to the doublet regimen. Furthermore, in several studies paclitaxel/carboplatin was associated with a lower incidence of neuropathy in comparison with paclitaxel/cisplatin but various authors observed no significant differences between both treatments. Nausea/vomiting and diarrhoea were the most

frequently reported gastrointestinal adverse events with paclitaxel-containing regimens. Significantly more patients experienced nausea and vomiting with cisplatin monotherapy compared to the paclitaxel/cisplatin. Paclitaxel/carboplatin showed a better tolerability than paclitaxel/cisplatin for non-haematological toxicities. The pattern of adverse events observed in the recent paclitaxel literature are consistent with those previously described during the BMS paclitaxel development programme. Discontinuation from study and deaths were as expected for patients with cancer. No unexpected toxicities or new safety issues were identified during these clinical trials.

Post-marketing experience

In the United States, paclitaxel is approved as Onxol (paclitaxel) Injection by IVAX; the product is identical to Paxene (paclitaxel) Injection, distributed by IVAX in Europe (IVAX Research Inc. 2003). For Onxol in total 12 Quarterly Adverse Drug Experience Reports are available, covering the period from 15/9/00 to 14/903. During this 3-year period the MAH received a total of 80 adverse events reports from approximately 30,000 to 40,000 patients exposed to Onxol™.
The marketing of Paxene started in May 2004. All previous PSURs submitted to the EMEA were based on published data and Onxol™ only.
In the renewal of the marketing authorisation application for Paxene submitted in April 2004, the 7th PSUR (which covered the period from July 1999 to January 2004 and also included the USA data from January 2000 to December 2003) summarised a total of 113 cases of adverse events from a total estimated patient exposure of approximately 77,000 patients. Fourteen were spontaneous reports received by Ivax Pharmaceuticals from healthcare professionals and the remaining 99 cases identified from the literature. Fifty-three cases were considered to be serious and 8 had a fatal outcome. Twenty-two serious unlabelled adverse events were reported.
The majority of the reported adverse events were labelled such as hypersensitivity reactions, haematological toxicity, nervous system disorders (i.e. neuropathy and encephalopathy), and nail changes. There were 33 reported adverse events, which are not listed in the currently approved SPC, which were addressed during the assessment of renewal. Subsequently, the SPC has been update accordingly.

Overall, based on the cumulative data collected in the respective periods, the safety profile of paclitaxel is considered to be acceptable.

Benefit -Risk
Based on the pivotal paclitaxel studies, and the subsequent literature, the efficacy of paclitaxel in combination with cisplatin in the treatment of non-small cell lung carcinoma (NSCLC) in patients who are not candidates for potentially curative surgery and/or radiation therapy has been demonstrated. The CHMP considered the benefit/risk profile of paclitaxel in the proposed indication is acceptable.