SCIENTIFIC DISCUSSION

Additional indication:

Treatment of patients with advanced carcinoma of the ovary (AOC) or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin as first-line treatment.

It has been demonstrated (see module 6: Scientific discussion, section 6) that paclitaxel marketed as Taxol and paclitaxel marked as Paxene have identical formulations on the basis of chemical/physical properties, in vitro behaviour (in particular on micelle formation) and in vivo pharmacokinetics. Therefore, it is acceptable for clinical data produced with Taxol to be applied in order to support new indications for Paxene.

Taxol (paclitaxel, MAH: Bristol Myers Squibb) was approved in the EU in 1993, and –among other indications- is currently approved for first-line treatment of ovarian cancer in patients with advanced carcinoma of the ovary or with residual disease (>1 cm) after initial laparotomy in combination with cisplatin.

Clinical aspects

Proof of efficacy of paclitaxel /cisplatin combinations as first-line chemotherapy in advanced ovarian carcinoma was based on two multicenter, randomised, controlled phase III trials (B-MS CA139-209, B-MS CA139-022; published by Piccart et al. 2000, McGuire et al. 1996). In addition to these data, which constitute the primary basis of the current submission, a literature update of the two new indications including 9 phase III clinical trials published since 1996 in the first-line therapy of advanced ovarian cancer) is provided. No new clinical pharmacological data is provided.

Clinical efficacy

In study CA139-022 410 patients were randomised to receive a maximum of 6 courses of paclitaxel (135 mg/m^2 over 24 h) followed by cisplatin (75 mg/m^2), or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2). Median progression free survival was significantly longer (p<0.001) with paclitaxel/cisplatin (17 months vs 13 months). Median survival also favoured the paclitaxel/cisplatin arm (36 months vs 24 months, p<0.001). There was no statistically significant difference between treatment arms in terms of clinical response (60% and 50% for paclitaxel/cisplatin and cyclophosphamide/cisplatin arms, respectively), although for pathological response rate there was a significant difference in favour of the paclitaxel/cisplatin arm (34% vs 20%, p=0.001).

In study CA139-209, 680 patients were randomised to receive paclitaxel (175 mg/m^2 over 3 h) followed by cisplatin (75 mg/m^2), or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2. Median progression free survival was 15.5 months in the paclitaxel/cisplatin arm vs 11.5 months in the cyclophosphamide/cisplatin arm (p=0.0005). This primary efficacy result was supported by the secondary efficacy endpoints: median survival 35.6 vs 25.8 months (p=0.0016), overall response rate 59% vs 45% (p=0.01), and complete response rate 41% vs 27% (p=0.01), for paclitaxel/cisplatin and cyclophosphamide/cisplatin, respectively.

Superiority of paclitaxel/cisplatin over standard therapy (cyclophosphamide/cisplatin) was demonstrated. Paclitaxel/cisplatin became the accepted standard first-line therapy for patients with advanced ovarian cancer or residual disease.

Long-term follow-up results from the two pivotal Taxol studies reported in a further study (Piccart et al. 2003, table 7.1). The median follow-up time of the two pivotal Taxol studies was approximately 3 years. 6.5-year follow-up data is now available. In each case, an 11% absolute gain in survival favouring the paclitaxel arm is shown; this advantage remains both statistically and clinically significant and supports a role for paclitaxel in first line chemotherapy for advanced ovarian cancer.

Table 1.:   Long term results of B-MS CA 139-022 and B-MS CA 139-209

	B-MS CA 139-022 (n=386 eligible patients)		B-MS CA 139-209 (n=680 randomised patients)	
	PTX/CIS	**CYC/CIS**	**PTX/CIS**	**CYC/CIS**
Proportion alive (%)	27	16	34	23
Relative hazard of death	0.70		0.75	
95 % CI	0.57-0.87		0.63-0.90	

PTX = paclitaxel; CIS = cisplatin; CYC = cyclophosphamide; CI = confidence interval

Literature Review

With modern cytoreductive surgery followed by a combination of platinum and paclitaxel, modest improvements in overall survival of advanced ovarian cancer were seen. However, despite increasing survival rates, advanced ovarian cancer is rarely cured and more than 50% of patients die within 5 years of diagnosis therefore, tolerability of treatment and quality of life (QoL) remain important issues and development of more effective therapy is a clear priority. With regards to paclitaxel/platinum-based therapy several issues remain to be clarified, including the optimal number of cycles, relative value of combined vs. sequential therapy with taxanes, the role of maintenance or consolidation and the most effective carboplatin dose (AUC 7.5 or lower). Results from 8 phase III studies, published since 2000, of efficacy and safety of paclitaxel-containing first line therapy of advanced ovarian cancer are presented in table 7.2 and discussed.

Table 2.: Overview of the clinical trials

Reference	Number of patients	Stage of ovarian cancer	Chemotherapy
Muggia et al. 2000 (n.r.)	614 (eligible) Test 1: 213 Test 2: 200 Control: 201	FIGO III, IV, mainly III; suboptimal	Test 1: PTX 200 mg/m^2, 24 h Test 2: CIS 100 mg/m^2; Control: PTX 135 mg/m^2, 24 h + CIS 75 mg/m^2
Du Bois et al. 2003b (non-inferiority trial)	783 (eligible) Test: 397 Control: 386	FIGO IIb-IV; mainly IIIc; optimal (stratum 1); suboptimal (stratum 2)	Test: PTX 185 mg/m^2, 3 h + CAR AUC 6 Control: PTX 185 mg/m^2, 3 h + CIS 75 mg/m^2
Ozols et al. 2003 (non-inferiority trial)	792 (eligible) Test: 392 Control: 400	stage III EOC; optimal	Test: PTX 175 mg/m^2, 3 h + CAR AUC 7.5 Control: PTX 135 mg/m^2, 24 h + CIS 75 mg/m^2
Neijt et al. 2000 (n.r.)	208 (eligible) Test: 100 Control 108	FIGO IIb-IV; mainly III; optimal and suboptimal	Test: PTX 175 mg/m^2, 3 h + CAR AUC 5 Control: PTX 175 mg/m^2, 3 h + CIS 75 mg/m^2
Markman et al. 2001 (n.r.)	462 (eligible) Test 235 Control: 227	stage III EOC; optimal	Test: CAR AUC 9 i.v. then PTX 135 mg/m^2, 24 h + CIS 100 mg/m^2 i.p. Control: PTX 135 mg/m^2, 24 h + CIS 75 mg/m^2

Reference	Number of patients	Stage of ovarian cancer	Chemotherapy
ICON Group 2002 (n.r.)	2,074 (eligible) Test: 710 Control 1: 421 Control 2: 943	FIGO Ic-IV; mainly III; suboptimal	Test: CAR AUC $\geq 5^{\#}$ or $6^{\#\#}$ + PTX 175 mg/m^2, 3 h Control 1: CYC 500 mg/m^2 + DOX 50 mg/m^2 + CIS 50 mg/m^2; Control 2 : CAR AUC $\geq 5^{\#}$ or $6^{\#\#}$
Kristensen et al. 2003 (n.r.)	872 (eligible) Test: 436 Control: 436	FIGO IIb-IV; mainly IIIc; suboptimal and optimal	Test: EPI 75 mg/m^2 + PTX 175 mg/m^2 3 h + CAR AUC 5 Control: PTX 175 mg/m^2 3 h + CAR AUC 5
Bolis et al. 2004 (n.r.)	494 (eligible) Test: 250 Control: 244	FIGO IIb-IV; mainly IIIc; suboptimal and optimal	Test: CAR AUC 6 + PTX 225 mg/m^2, 3 h Control: CAR AUC 6 + PTX 175 mg/m^2, 3 h

$^{\#}$ = GFR determined by radioisotope method or 24-h urine; $^{\#\#}$ = GFR determined by Cockcroft formula

n.r. = not reported; CIS = cisplatin; PTX = paclitaxel; CYC = cyclophosphamide; CAR = carboplatin; EPI = epirubicin; DOX = doxorubicin

Clinical response was evaluated in 5 controlled studies.
For paclitaxel/cisplatin, the overall response rate was 61-81%, with CR rates of 35- 43%. The highest response rates were achieved with paclitaxel/cisplatin (185 mg/m^2 over 3 h/75 mg/m^2); however, no additional survival benefit was observed. These results are consistent with those observed in the pivotal BMS studies: overall response rates of 60% and 59% (B-MS CA139-022 and B-MS CA139-209) respectively.
For paclitaxel/carboplatin-containing regimens, the overall response rates range from 65-80%, with 31-55% of patients achieving CR. An increased dose of paclitaxel (185 mg/m^2 over 3 h) combined with carboplatin AUC 6 did not result in higher response rates. (Bolis et al. 2004).

In comparison to paclitaxel/carboplatin, paclitaxel/cisplatin response was significantly better in only one study (Du Bois et al. 2003b) and no survival benefit was observed. In another clinical trial no significant differences were observed between paclitaxel/cisplatin and paclitaxel/carboplatin (Neijt et al. 2000). Response rates with paclitaxel monotherapy were significantly lower. There were no significant differences between paclitaxel/carboplatin and the new triple combination paclitaxel/carboplatin/epirubicin.

Survival and Progression-Free Survival

Overall survival and progression-free survival were determined in 6 studies; 4-year rates were reported by Bolis et al. (2004). Survival parameters are defined as primary endpoint in 5/7 trials. The results are summarised in Table 7. 3.

For paclitaxel/cisplatin regimens, OS ranged from 26.3- 52.2 months, PFS from 14.1-22.2 months. Two dosage regimes of Paxene are proposed: 175 mg/m^2 administered as a 3-hour, or 135 mg/m^2 as a 24-hour i.v. infusion, followed by cisplatin 75 mg/m^2 every three weeks. Comparable results were obtained with paclitaxel/cisplatin 135 mg/m^2 over 24 h/75 mg/m^2 (OS 26.3- 52.2 months, PFS 14.1-22.2 months) and 175 mg/m^2 over 3 h/75 mg/m^2 (OS 30-36.1 months, PFS 16-17.3 months). These results are consistent with those observed in the pivotal BMS studies paclitaxel/cisplatin-treated patients: median OS durations of 38 and 35.6 months (B-MS CA139-022 and B-MS CA139-209, respectively). The corresponding PFS figures were 18 and 15.5 months, respectively. An increased dose of paclitaxel (185 mg/m^2 over 3 h) in combination with cisplatin (75 mg/m^2) does not result in a survival benefit (Du Bois et al. 2003b). The best results (OS 52.2 months; PFS 22.2 months) are reported by Markman et al. (2001), who treated optimally debulked patients with 135 mg/m^2 paclitaxel over 24 h, and 75 mg/m^2 cisplatin.

For paclitaxel/carboplatin-containing regimens (175 mg/m^2/AUC 5-7.5), OS of 32.0-57.4 months and PFS from 16.0-20.7 months) are reported. Increasing the dose of paclitaxel (185 mg/m^2 over 3 h) in combination with carboplatin AUC 6 or high-dose paclitaxel/carboplatin regimen (225 mg/m^2 over 3 h/AUC 6), Bolis et al. (2004), did not lead to a survival benefit. The best results (OS 57.4 months; PFS 20.7 months) are reported by Ozols et al. (2003), who treated optimally debulked patients with 175 mg/m^2 paclitaxel over 3 h, and carboplatin AUC 7.5. Three studies concluded that paclitaxel/ carboplatin achieved comparable efficacy paclitaxel/cisplatin (Du Bois et al. 2003b, Ozols et al. 2003 and Neijt et al. 2000). It was associated with better gastrointestinal and neurological tolerability but higher frequency of haematological toxicity (neutropenia, ≥ grade 2 thrombocytopenia) and better QoL and should be considered an important alternative to standard first-line chemotherapy in patients with advanced ovarian cancer.

In a single study of 2074 patients (ICON Group 2002) comparing paclitaxel/carboplatin vs. carboplatin monotherapy or cyclophosphamide/doxorubicin/cisplatin similar efficacy was noted for carboplatin alone and combination therapy, and carboplatin alone was associated with fewer toxicities. It was concluded that the efficacy of single-agent carboplatin and triple therapy equals that of the standard therapy as first-line treatment for women requiring chemotherapy for ovarian cancer. The favourable toxicity profile of carboplatin monotherapy suggests that this drug is a reasonable option as first-line chemotherapy for ovarian cancer. Further investigations are required to demonstrate the potential advantage of carboplatin alone over standard therapy.

In comparison to paclitaxel/cisplatin, the corresponding carboplatin-containing regimen showed generally comparable results with respect to survival criteria but a better non-haematological toxicity profile and in a single study a better QoL. Thus paclitaxel/carboplatin may be considered a preferable first-line therapy for women with advanced ovarian cancer.

In comparison to paclitaxel monotherapy (200 mg/m^2 over 24 h), OS (25.9 vs 26.3 months) and PFS (10.8 vs 14.1 months) are longer for combination paclitaxel/cisplatin. In comparison to paclitaxel/platinum, cisplatin monotherapy (100 mg/m^2) or carboplatin monotherapy (AUC 5 or 6) lead to comparable survival and progression-free survival times.

Table .3. Effects of paclitaxel-containing regimens on survival and progression-free survival

Treatment arms[&,a]	Overall survival (months)	PFS (months)	Reference
PTX PTX 200, 24 h vs	25.9	10.8	Muggia et al. 2000
CIS CIS 100 vs	30.2	16.4	
PTX/CIS PTX 135, 24 h + CIS 75	26.3	14.1	
PTX/CIS PTX 185, 3 h + CIS 75 vs	44.1	19.1	Du Bois et al. 2003b
PTX/CAR PTX 185, 3 h + CAR AUC 6	43.3	17.2	
PTX/CIS PTX 175, 3 h + CIS 75 vs	30	16	Neijt et al. 2000
PTX/CAR PTX 175, 3 h + CAR AUC 5	32	16	

Treatment arms[&,a]	Overall survival (months)	PFS (months)	Reference
CAR followed by PTX/CIS: CAR AUC 9 i.v. + PTX 135, 24 h + CIS 100 i.p. vs PTX/CIS: PTX 135, 24 h + CIS 75	63.2 52.2 p=0.05	27.9 22.2 p=0.01	Markman et al. 2001
Control: PTX/CAR: PTX 175, 3 h + CAR AUC ≥ 5[#] or 6[##] vs Test: CYC/DOX/CIS: CYC 500 + DOX 50 + CIS 50 or CAR: CAR AUC ≥ 5[#] or 6[##]	36.1 35.4	17.3 16.1	ICON Group 2002
PTX HD/CAR: CAR AUC 6 + PTX 225 over 3 h vs PTX LD/CAR: CAR AUC 6 + PTX 175 over 3 h	4-year survival rate (%) 47.3 46.2	4 y PFS rate (%) 39.2 41.5	Bolis et al. 2004

[&] PTX, CIS, EPI, DOX, CYC dose in mg/m^2, [a] CAR AUC in mg/ml/min, [#] GFR determined by radioisotope method or 24-h urine; [##] GFR determined by Cockcroft formula. AUC: area under curve, CAR: carboplatin, CIS: cisplatin, CYC: cyclophosphamide, DOX: doxorubicin, EPI: epirubicin, HD: high dose; LD: low dose; PFS: progression-free survival, PTX: paclitaxel

New combinations

New combinations using gemcitabine, topotecan[1] or anthracyclines are currently being investigated. To date, only one full report has been published comparing paclitaxel/carbopatin with paclitaxel/epirubicin/carboplatin. However, only results of response are available CR 55% vs. 65% respectively; survival results are still awaited.

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). Detailed clinical safety data from the publications of the pivotal studies with Taxol in ovarian cancer and NSCLC and supportive safety data from literature review on on paclitaxel-containing combinations in 20 additional studies are provided in section 8.

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[1] At least two-phase III studies are currently ongoing, comparing paclitaxel/carboplatin with paclitaxel/carboplatin followed by topotecan or paclitaxel/carboplatin with paclitaxel/carboplatin/gemcitabine (Du Bois et al. 2003a).

The severity of neutropenia, febrile neuropenia, alopecia, and peripheral neurotoxicity was significantly greater (p≤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.

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.

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 (EMEA/H/C/216/R/22), 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 assessment

Based primarily on the data from two pivotal BMS studies (B-MS CA139-022 and B-MS CA139-209), in which the superiority of paclitaxel/cisplatin over cyclophosphamide/cisplatin was demonstrated, paclitaxel/cisplatin has become the accepted standard first-line therapy for patients with advanced ovarian cancer or with residual disease. Subsequent studies in which paclitaxel/cisplatin has been evaluated support the pivotal BMS data and confirm that paclitaxel-containing combinations, paclitaxel/cisplatin and paclitaxel/carboplatin, produce a favourable treatment response, improvement

in survival, and progression-free survival in patients with advanced ovarian cancer. Therefore paclitaxel plus cisplatin is still considered as first-line therapy in ovarian cancer.

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.

Based on the pivotal paclitaxel studies, and the subsequent literature, the efficacy of paclitaxel in combination with cisplatin in the treatment of patients with advanced carcinoma of the ovary or with residual disease (> 1 cm) after initial laparotomy (first line chemotherapy) has been demonstrated. The CHMP considered the benefit/risk profile of paclitaxel in the proposed indication is acceptable.