TABLE 9
SELECTED ADVERSE EVENTS IN GERIATRIC PATIENTS RECEIVING TAXOL IN CLINICAL STUDIES

	Patients (n/total [%])			
	Neutropenia (Grade IV)		Peripheral Neuropathy (Grades III/IV)	
INDICATION	Age (y)		Age (y)	
(Study/Regimen)	≥65	<65	≥65	<65
• ***OVARIAN Cancer***				
(Intergroup First-Line/T175/3 c75[a])	34/83 (41)	78/252 (31)	24/84 (29)*[b]	46/255 (18)[b]
(GOG-111 First-Line/T135/24 c75[a])	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
(Phase 3 Second-Line/T175/3[c])	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
(Phase 3 Second-Line/T175/24[c])	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
(Phase 3 Second-Line/T135/3[c])	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
(Phase 3 Second-Line/T135/24[c])	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
(Phase 3 Second-Line Pooled)	47/82 (57)*	141/319 (44)	1/83 (1)	2/320 (1)
• ***Adjuvant BREAST Cancer***				
(Intergroup/AC followed by T[d])	56/102 (55)	734/1468 (50)	5/102 (5)[e]	46/1468 (3)[e]
• ***BREAST Cancer After Failure of Initial Therapy***				
(Phase 3/T175/3[c])	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
(Phase 3/T135/3[c])	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
• ***Non-Small Cell LUNG Cancer***				
(ECOG/T135/24 c75[a])	58/71 (82)	86/124 (69)	9/71 (13)[f]	16/124 (13)[f]
(Phase 3/T175/3 c80[a])	37/89 (42)*	56/267 (21)	11/91 (12)*	11/271 (4)

* $p<0.05$

[a] TAXOL dose in mg/m^2/infusion duration in hours; cisplatin doses in mg/m^2.

[b] Peripheral neuropathy was included within the neurotoxicity category in the Intergroup First-Line Ovarian Cancer study (see **TABLE 11**).

[c] TAXOL dose in mg/m^2/infusion duration in hours.

[d] TAXOL (T) following 4 courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

[e] Peripheral neuropathy reported as neurosensory toxicity in the Intergroup Adjuvant Breast Cancer study (see **TABLE 13**).

[f] Peripheral neuropathy reported as neurosensory toxicity in the ECOG NSCLC study (see **TABLE 15**).

Information for Patients: (See **Patient Information Leaflet.**)

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-

agent TAXOL. Two hundred and seventy-five patients were treated in 8, Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared 2 doses (135 or 175 mg/m^2) and 2 schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

TABLE 10

SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT TAXOL

		Percent of Patients (n=812)
• ***Bone Marrow***		
—Neutropenia	<2000/mm^3	90
	<500/mm^3	52
—Leukopenia	<4000/mm^3	90
	<1000/mm^3	17
—Thrombocytopenia	<100,000/mm^3	20
	<50,000/mm^3	7
—Anemia	<11 g/dL	78
	<8 g/dL	16
—Infections		30
—Bleeding		14
—Red Cell Transfusions		25
—Platelet Transfusions		2
• ***Hypersensitivity Reaction***[b]		
—All		41
—Severe[†]		2
• ***Cardiovascular***		
—Vital Sign Changes[c]		
—Bradycardia (n=537)		3
—Hypotension (n=532)		12
—Significant Cardiovascular Events		1
• ***Abnormal ECG***		
—All Pts		23
—Pts with normal baseline (n=559)		14
• ***Peripheral Neuropathy***		
—Any symptoms		60
—Severe symptoms[†]		3
• ***Myalgia/Arthralgia***		
—Any symptoms		60
—Severe symptoms[†]		8
• ***Gastrointestinal***		
—Nausea and vomiting		52
—Diarrhea		38
—Mucositis		31
• ***Alopecia***		87
• ***Hepatic*** (Pts with normal baseline and on study data)		
—Bilirubin elevations (n=765)		7
—Alkaline phosphatase elevations (n=575)		22
—AST (SGOT) elevations (n=591)		19
• ***Injection Site Reaction***		13

[a] Based on worst course analysis.

[b] All patients received premedication.

[c] During the first 3 hours of infusion.

[†] Severe events are defined as at least Grade III toxicity.

None of the observed toxicities were clearly influenced by age.

Disease-Specific Adverse Event Experiences

First-Line Ovary in Combination: For the 1084 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy studies, **TABLE 11** shows the incidence of important adverse events. For both studies, the analysis of safety was based on all courses of therapy (6 courses for the GOG-111 study and up to 9 courses for the Intergroup study).

TABLE 11
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

		Percent of Patients			
		Intergroup		**GOG-111**	
		T175/3[b] c75[c] (n=339)	C750[c] c75[c] (n=336)	T135/24[b] c75[c] (n=196)	C750[c] c75[c] (n=213)
• ***Bone Marrow***					
—Neutropenia	<2000/mm^3	91[d]	95[d]	96	92
	<500/mm^3	33[d]	43[d]	81[d]	58[d]
—Thrombocytopenia	<100,000/mm^3[e]	21[d]	33[d]	26	30
	<50,000/mm^3	3[d]	7[d]	10	9
—Anemia	<11 g/dL[f]	96	97	88	86
	<8 g/dL	3[d]	8[d]	13	9
—Infections		25	27	21	15
—Febrile Neutropenia		4	7	15[d]	4[d]
• ***Hypersensitivity Reaction***					
—All		11[d]	6[d]	8[d,g]	1[d,g]
—Severe[†]		1	1	3[d,g]	—[d,g]
• ***Neurotoxicity***[h]					
—Any symptoms		87[d]	52[d]	25	20
—Severe symptoms[†]		21[d]	2[d]	3[d]	—[d]
• ***Nausea and Vomiting***					
—Any symptoms		88	93	65	69
—Severe symptoms[†]		18	24	10	11
• ***Myalgia/Arthralgia***					
—Any symptoms		60[d]	27[d]	9[d]	2[d]
—Severe symptoms[†]		6[d]	1[d]	1	—
• ***Diarrhea***					
—Any symptoms		37[d]	29[d]	16[d]	8[d]
—Severe symptoms[†]		2	3	4	1
• ***Asthenia***					
—Any symptoms		NC	NC	17[d]	10[d]
—Severe symptoms[†]		NC	NC	1	1
• ***Alopecia***					
—Any symptoms		96[d]	89[d]	55[d]	37[d]
—Severe symptoms[†]		51[d]	21[d]	6	8

[a] Based on worst course analysis.

[b] TAXOL (T) dose in mg/m^2/infusion duration in hours.

[c] Cyclophosphamide (C) or cisplatin (c) dose in mg/m^2.

[d] $p<0.05$ by Fisher exact test.

[e] <130,000/mm^3 in the Intergroup study.

[f] <12 g/dL in the Intergroup study.

[g] All patients received premedication.

[h] In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and in the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms.

[†] Severe events are defined as at least Grade III toxicity.

NC Not Collected

Second-Line Ovary: For the 403 patients who received single-agent TAXOL in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

TABLE 12
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

		Percent of Patients			
		175/3[b] (n=95)	175/24[b] (n=105)	135/3[b] (n=98)	135/24[b] (n=105)
• ***Bone Marrow***					
—Neutropenia	<2000/mm^3	78	98	78	98
	<500/mm^3	27	75	14	67
—Thrombocytopenia	<100,000/mm^3	4	18	8	6
	<50,000/mm^3	1	7	2	1
—Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
—Infections		26	29	20	18
• ***Hypersensitivity Reaction***[c]					
—All		41	45	38	45
—Severe[†]		2	0	2	1
• ***Peripheral Neuropathy***					
—Any symptoms		63	60	55	42
—Severe symptoms[†]		1	2	0	0
• ***Mucositis***					
—Any symptoms		17	35	21	25
—Severe symptoms[†]		0	3	0	2

[a] Based on worst course analysis.
[b] TAXOL dose in mg/m^2/infusion duration in hours.
[c] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose related, but schedule did not appear to affect the incidence.

Adjuvant Breast: For the Phase 3 adjuvant breast carcinoma study, the following table shows the incidence of important severe adverse events for the 3121 patients (total population) who were evaluable for safety as well as for a group of 325 patients (early population) who, per the study protocol, were monitored more intensively than other patients.

TABLE 13
FREQUENCY[a] OF IMPORTANT SEVERE[b] ADVERSE EVENTS IN THE PHASE 3 ADJUVANT BREAST CARCINOMA STUDY

	Percent of Patients			
	Early Population		Total Population	
	AC[c] (n=166)	AC[c] followed by T[d] (n=159)	AC[c] (n=1551)	AC[c] followed by T[d] (n=1570)
• ***Bone Marrow***[e]				
—Neutropenia <500/mm^3	79	76	48	50
—Thrombocytopenia <50,000/mm^3	27	25	11	11
—Anemia <8 g/dL	17	21	8	8
—Infections	6	14	5	6
—Fever Without Infection	—	3	<1	1
• ***Hypersensitivity Reaction***[f]	1	4	1	2
• ***Cardiovascular Events***	1	2	1	2
• ***Neuromotor Toxicity***	1	1	<1	1
• ***Neurosensory Toxicity***	—	3	<1	3
• ***Myalgia/Arthralgia***	—	2	<1	2
• ***Nausea/Vomiting***	13	18	8	9
• ***Mucositis***	13	4	6	5

[a] Based on worst course analysis.

[b] Severe events are defined as at least Grade III toxicity.

[c] Patients received 600 mg/m^2 cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m^2, 75 mg/m^2, or 90 mg/m^2 (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for 4 courses.

[d] TAXOL (T) following 4 courses of AC at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

[e] The incidence of febrile neutropenia was not reported in this study.

[f] All patients were to receive premedication.

The incidence of an adverse event for the total population likely represents an underestimation of the actual incidence given that safety data were collected differently based on enrollment cohort. However, since safety data were collected consistently across regimens, the safety of the sequential addition of TAXOL (paclitaxel) following AC therapy may be compared with AC therapy alone. Compared to patients who received AC alone, patients who received AC followed by TAXOL experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional 4 courses of treatment with TAXOL, 2 deaths (0.1%) were attributed to treatment. During TAXOL treatment, Grade IV neutropenia was reported for 15% of patients, Grade II/III neurosensory toxicity for 15%, Grade II/III myalgias for 23%, and alopecia for 46%.

The incidences of severe hematologic toxicities, infections, mucositis, and cardiovascular events increased with higher doses of doxorubicin.

Breast Cancer After Failure of Initial Chemotherapy: For the 458 patients who received single-agent TAXOL in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a 3-hour infusion).

TABLE 14
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY OF BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

		Percent of Patients	
		175/3[b] (n=229)	135/3[b] (n=229)
• ***Bone Marrow***			
—Neutropenia	<2000/mm^3	90	81
	<500/mm^3	28	19
—Thrombocytopenia	<100,000/mm^3	11	7
	<50,000/mm^3	3	2
—Anemia	<11 g/dL	55	47
	<8 g/dL	4	2
—Infections		23	15
—Febrile Neutropenia		2	2
• ***Hypersensitivity Reaction***[c]			
—All		36	31
—Severe[†]		0	<1
• ***Peripheral Neuropathy***			
—Any symptoms		70	46
—Severe symptoms[†]		7	3
• ***Mucositis***			
—Any symptoms		23	17
—Severe symptoms[†]		3	<1

[a] Based on worst course analysis.
[b] TAXOL dose in mg/m^2/infusion duration in hours.
[c] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

First-Line NSCLC in Combination: In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either TAXOL (T) 135 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2, TAXOL (T) 250 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2 with G-CSF support, or cisplatin (c) 75 mg/m^2 on day 1, followed by etoposide (VP) 100 mg/m^2 on days 1, 2, and 3 (control).

The following table shows the incidence of important adverse events.

TABLE 15
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY FOR FIRST-LINE NSCLC

		Percent of Patients		
		T135/24[b] c75 (n=195)	T250/24[c] c75 (n=197)	VP100[d] c75 (n=196)
• ***Bone Marrow***				
—Neutropenia	<2000/mm^3	89	86	84
	<500/mm^3	74[e]	65	55
—Thrombocytopenia	< normal	48	68	62
	<50,000/mm^3	6	12	16
—Anemia	< normal	94	96	95
	<8 g/dL	22	19	28
—Infections		38	31	35
• ***Hypersensitivity Reaction***[f]				
—All		16	27	13
—Severe[†]		1	4[e]	1
• ***Arthralgia/Myalgia***				
—Any symptoms		21[e]	42[e]	9
—Severe symptoms[†]		3	11	1
• ***Nausea/Vomiting***				
—Any symptoms		85	87	81
—Severe symptoms[†]		27	29	22
• ***Mucositis***				
—Any symptoms		18	28	16
—Severe symptoms[†]		1	4	2
• ***Neuromotor Toxicity***				
—Any symptoms		37	47	44
—Severe symptoms[†]		6	12	7
• ***Neurosensory Toxicity***				
—Any symptoms		48	61	25
—Severe symptoms[†]		13	28[e]	8
• ***Cardiovascular Events***				
—Any symptoms		33	39	24
—Severe symptoms[†]		13	12	8

[a] Based on worst course analysis.
[b] TAXOL (T) dose in mg/m^2/infusion duration in hours; cisplatin (c) dose in mg/m^2.
[c] TAXOL dose in mg/m^2/infusion duration in hours with G-CSF support; cisplatin dose in mg/m^2.
[d] Etoposide (VP) dose in mg/m^2 was administered IV on days 1, 2, and 3; cisplatin dose in mg/m^2.
[e] $p<0.05$.
[f] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

Toxicity was generally more severe in the high-dose TAXOL treatment arm (T250/c75) than in the low-dose TAXOL arm (T135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose TAXOL arm experienced more arthralgia/myalgia of any grade

and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

Kaposi's Sarcoma: The following table shows the frequency of important adverse events in the 85 patients with KS treated with 2 different single-agent TAXOL (paclitaxel) regimens.

TABLE 16
FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE AIDS-RELATED KAPOSI'S SARCOMA STUDIES

		Percent of Patients	
		Study CA139-174 TAXOL 135/3[b] q 3 wk (n=29)	Study CA139-281 TAXOL 100/3[b] q 2 wk (n=56)
• ***Bone Marrow***			
—Neutropenia	<2000/mm^3	100	95
	<500/mm^3	76	35
—Thrombocytopenia	<100,000/mm^3	52	27
	<50,000/mm^3	17	5
—Anemia	<11 g/dL	86	73
	<8 g/dL	34	25
—Febrile Neutropenia		55	9
• ***Opportunistic Infection***			
—Any		76	54
—Cytomegalovirus		45	27
—Herpes Simplex		38	11
—*Pneumocystis carinii*		14	21
—*M. avium intracellulare*		24	4
—Candidiasis, esophageal		7	9
—Cryptosporidiosis		7	7
—Cryptococcal meningitis		3	2
—Leukoencephalopathy		—	2
• ***Hypersensitivity Reaction***[c]			
—All		14	9
• ***Cardiovascular***			
—Hypotension		17	9
—Bradycardia		3	—
• ***Peripheral Neuropathy***			
—Any		79	46
—Severe[†]		10	2
• ***Myalgia/Arthralgia***			
—Any		93	48
—Severe[†]		14	16
• ***Gastrointestinal***			
—Nausea and Vomiting		69	70
—Diarrhea		90	73
—Mucositis		45	20
• ***Renal (creatinine elevation)***			
—Any		34	18
—Severe[†]		7	5
• ***Discontinuation for drug toxicity***		7	16

[a] Based on worst course analysis.
[b] TAXOL dose in mg/m^2/infusion duration in hours.
[c] All patients received premedication.
[†] Severe events are defined as at least Grade III toxicity.

As demonstrated in this table, toxicity was more pronounced in the study utilizing TAXOL (paclitaxel) at a dose of 135 mg/m^2 every 3 weeks than in the study utilizing

TAXOL at a dose of 100 mg/m^2 every 2 weeks. Notably, severe neutropenia (76% vs 35%), febrile neutropenia (55% vs 9%), and opportunistic infections (76% vs 54%) were more common with the former dose and schedule. The differences between the 2 studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

Adverse Event Experiences by Body System

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent TAXOL in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received TAXOL in combination with cisplatin or in patients with breast cancer who received TAXOL after doxorubicin/cyclophosphamide in the adjuvant setting and that occurred with a difference that was clinically significant in these populations are also described. The frequency and severity of important adverse events for the Phase 3 ovarian carcinoma, breast carcinoma, NSCLC, and the Phase 2 Kaposi's sarcoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving TAXOL for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections (including opportunistic infections, see **TABLE 16**), and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described. Elevated liver function tests and renal toxicity have a higher incidence in KS patients as compared to patients with solid tumors.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of TAXOL. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm^3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27%

at a dose of 175 mg/m^2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

In the study where TAXOL was administered to patients with ovarian carcinoma at a dose of 135 mg/m^2/24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the TAXOL plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the TAXOL plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the TAXOL/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When TAXOL followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (TAXOL 135 mg/m^2/24 hours followed by cisplatin) and 65% (TAXOL 250 mg/m^2/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m^2 or 175 mg/m^2 given as 3-hour infusions, respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.) The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See **DOSAGE AND ADMINISTRATION**.)

Thrombocytopenia was reported. Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were

reported in 10% of the patients; no patients treated with the 3-hour infusion received platelet transfusions. In the adjuvant breast carcinoma trial, the incidence of severe thrombocytopenia and platelet transfusions increased with higher doses of doxorubicin.

Anemia (Hb <11 g/dL) was observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to TAXOL (see **WARNINGS** and **PRECAUTIONS: Hypersensitivity Reactions**). The frequency and severity of HSRs were not affected by the dose or schedule of TAXOL administration. In the Phase 3 second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of TAXOL infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain, and tachycardia. Abdominal pain, pain in the extremities, diaphoresis, and hypertension were also noted.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Chills, shock, and back pain in association with hypersensitivity reactions have been reported.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to single-agent TAXOL (paclitaxel) occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension, and venous thrombosis. One of the patients with syncope treated with TAXOL at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy, and complete AV block requiring pacemaker placement. Among patients with NSCLC treated with TAXOL in combination with cisplatin in the Phase 3 study, significant cardiovascular events occurred in 12 to 13%. This apparent increase in cardiovascular events is possibly due to an increase in cardiovascular risk factors in patients with lung cancer.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia, and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported. Congestive heart failure, including cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure, has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See **PRECAUTIONS: Drug Interactions**.)

Atrial fibrillation and supraventricular tachycardia have been reported.

Respiratory: Interstitial pneumonia, lung fibrosis, and pulmonary embolism have been reported. Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Pleural effusion and respiratory failure have been reported.

Neurologic: The assessment of neurologic toxicity was conducted differently among the studies as evident from the data reported in each individual study (see **TABLES 10–16**). Moreover, the frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent TAXOL. Peripheral neuropathy was observed in 60%

of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Paresthesia commonly occurs in the form of hyperesthesia. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34 to 51% from course 2 to 10. Peripheral neuropathy was the cause of TAXOL discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of TAXOL discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for TAXOL therapy.

In the Intergroup first-line ovarian carcinoma study (see **TABLE 11**), neurotoxicity included reports of neuromotor and neurosensory events. The regimen with TAXOL 175 mg/m^2 given by 3-hour infusion plus cisplatin 75 mg/m^2 resulted in greater incidence and severity of neurotoxicity than the regimen containing cyclophosphamide and cisplatin, 87% (21% severe) versus 52% (2% severe), respectively. The duration of grade III or IV neurotoxicity cannot be determined with precision for the Intergroup study since the resolution dates of adverse events were not collected in the case report forms for this trial and complete follow-up documentation was available only in a minority of these patients. In the GOG first-line ovarian carcinoma study, neurotoxicity was reported as peripheral neuropathy. The regimen with TAXOL 135 mg/m^2 given by 24-hour infusion plus cisplatin 75 mg/m^2 resulted in an incidence of neurotoxicity that was similar to the regimen containing cyclophosphamide plus cisplatin, 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in the Intergroup and GOG trials suggests that when TAXOL is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a TAXOL dose of 175 mg/m^2 given by 3-hour infusion (21%) than at a dose of 135 mg/m^2 given by 24-hour infusion (3%).

In patients with NSCLC, administration of TAXOL followed by cisplatin resulted in a greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent TAXOL. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving TAXOL 135 mg/m^2 by 24-hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide (see **TABLE 15**).

Other than peripheral neuropathy, serious neurologic events following TAXOL administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Autonomic neuropathy resulting in paralytic ileus has been reported. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage. Postmarketing reports of ototoxicity (hearing loss and tinnitus) have also been received.

Convulsions, dizziness, and headache have been reported.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of TAXOL and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred 2 or 3 days after TAXOL administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of TAXOL administration. Among patients with normal baseline liver function 7%, 22%, and 19% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Prolonged exposure to TAXOL was not associated with cumulative hepatic toxicity.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Renal: Among the patients treated for Kaposi's sarcoma with TAXOL, 5 patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other 4 patients had renal insufficiency with reversible elevations of serum creatinine.

Patients with gyneocological cancers treated with TAXOL and cisplatin may have an increased risk of renal failure with the combination therapy of paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

In patients with poor-risk AIDS-related Kaposi's sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79%, and 28% of patients, respectively. One-third of

patients with Kaposi's sarcoma complained of diarrhea prior to study start. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.)

In the first-line Phase 3 ovarian carcinoma studies, the incidence of nausea and vomiting when TAXOL was administered in combination with cisplatin appeared to be greater compared with the database for single-agent TAXOL in ovarian and breast carcinoma. In addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no difference for severe diarrhea in these studies.

Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, dehydration, esophagitis, constipation, and ascites have been reported. Neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, was observed in patients treated with TAXOL alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, ie, "recall," has been reported.

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to TAXOL-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with TAXOL administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Skin abnormalities related to radiation recall as well as maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Reports of asthenia and malaise have been received as part of the continuing surveillance of TAXOL safety. In the Phase 3 trial of TAXOL 135 mg/m^2 over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/cisplatin.

Conjunctivitis, increased lacrimation, anorexia, confusional state, photopsia, visual floaters, vertigo, and increase in blood creatinine have been reported.

Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE

There is no known antidote for TAXOL (paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (see **PRECAUTIONS: Pediatric Use**).

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted TAXOL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to TAXOL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before TAXOL, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to TAXOL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before TAXOL.

For patients with **carcinoma of the ovary**, the following regimens are recommended (see **CLINICAL STUDIES: Ovarian Carcinoma**):

1) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered (see **TABLE 11** in **ADVERSE REACTIONS: Disease-Specific Adverse Event Experiences**).
   a. TAXOL administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or
   b. TAXOL administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.
2) In patients previously treated with chemotherapy for carcinoma of the ovary, TAXOL has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is TAXOL 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with **carcinoma of the breast**, the following regimens are recommended (see **CLINICAL STUDIES: Breast Carcinoma**):

1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is TAXOL, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used 4 courses of doxorubicin and cyclophosphamide (see **CLINICAL STUDIES: Breast Carcinoma**).

2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, TAXOL at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with **non-small cell lung carcinoma**, the recommended regimen, given every 3 weeks, is TAXOL administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with **AIDS-related Kaposi's sarcoma**, TAXOL administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m^2/week). In the 2 clinical trials evaluating these schedules (see **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**), the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2 every 2 weeks).

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients: