

**TABLE 4**  
SUBSET ANALYSES—ADJUVANT BREAST CARCINOMA STUDY

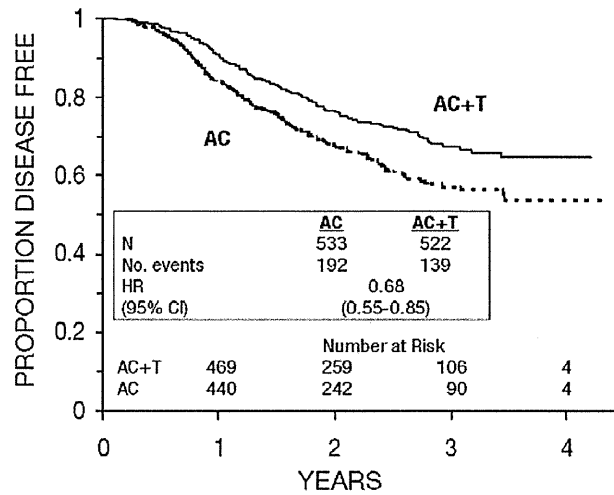
Patient Subset	No. of Patients	Disease-Free Survival		Overall Survival	
		No. of Recurrences	Hazard Ratio (95% CI)	No. of Deaths	Hazard Ratio (95% CI)
• <i>No. of Positive Nodes</i>					
1–3	1449	221	0.72 (0.55–0.94)	107	0.76 (0.52–1.12)
4–9	1310	274	0.78 (0.61–0.99)	148	0.66 (0.47–0.91)
10+	360	129	0.93 (0.66–1.31)	87	0.90 (0.59–1.36)
• <i>Tumor Size (cm)</i>					
≤2	1096	153	0.79 (0.57–1.08)	67	0.73 (0.45–1.18)
>2 and ≤5	1611	358	0.79 (0.64–0.97)	201	0.74 (0.56–0.98)
>5	397	111	0.75 (0.51–1.08)	72	0.73 (0.46–1.16)
• <i>Menopausal Status</i>					
Pre	1929	374	0.83 (0.67–1.01)	187	0.72 (0.54–0.97)
Post	1183	250	0.73 (0.57–0.93)	155	0.77 (0.56–1.06)
• <i>Receptor Status</i>					
Positive <sup>a</sup>	2066	293	0.92 (0.73–1.16)	126	0.83 (0.59–1.18)
Negative/Unknown <sup>b</sup>	1055	331	0.68 (0.55–0.85)	216	0.71 (0.54–0.93)

<sup>a</sup> Positive for either estrogen or progesterone receptors.

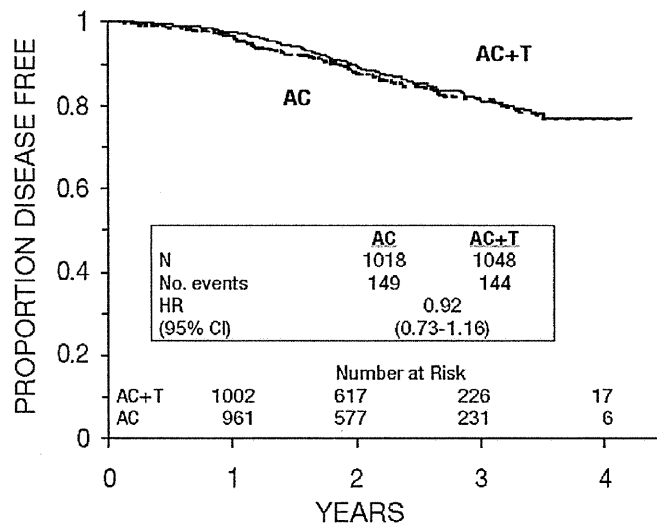
<sup>b</sup> Negative or missing for both estrogen and progesterone receptors (both missing: n=15).

These retrospective subgroup analyses suggest that the beneficial effect of TAXOL (paclitaxel) is clearly established in the receptor-negative subgroup, but the benefit in receptor-positive patients is not yet clear. With respect to menopausal status, the benefit of TAXOL is consistent (see **TABLE 4** and **FIGURES 5–8**).

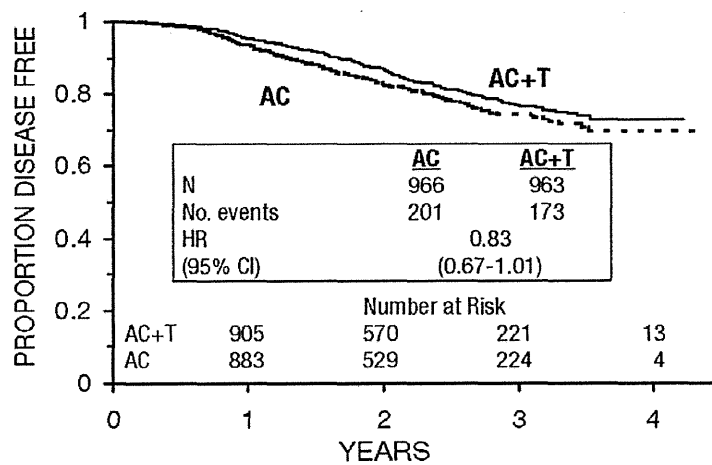
**FIGURE 5**  
**DISEASE-FREE SURVIVAL—RECEPTOR STATUS NEGATIVE/UNKNOWN**  
**AC VERSUS AC+T**



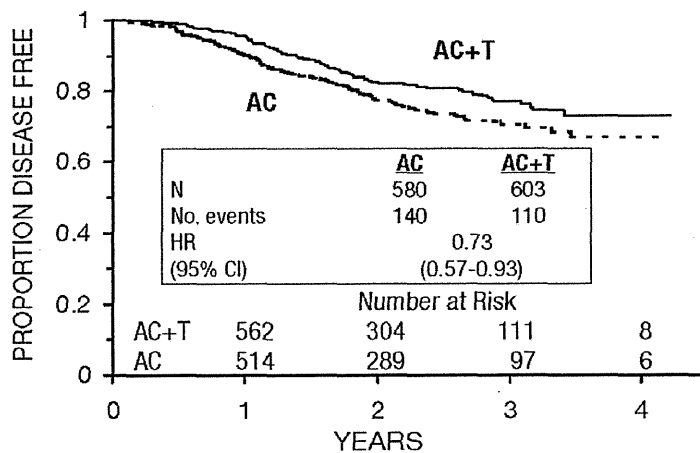
**FIGURE 6**  
**DISEASE-FREE SURVIVAL—RECEPTOR STATUS POSITIVE**  
**AC VERSUS AC+T**



**FIGURE 7**  
**DISEASE-FREE SURVIVAL—PREMENOPAUSAL**  
**AC VERSUS AC+T**



**FIGURE 8**  
**DISEASE-FREE SURVIVAL—POSTMENOPAUSAL**  
**AC VERSUS AC+T**



The adverse event profile for the patients who received TAXOL subsequent to AC was consistent with that seen in the pooled analysis of data from 812 patients (TABLE 10) treated with single-agent TAXOL in 10 clinical studies. These adverse events are described in the ADVERSE REACTIONS section in tabular (TABLES 10 and 13) and narrative form.

### **After Failure of Initial Chemotherapy**

Data from 83 patients accrued in 3, Phase 2 open-label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of TAXOL in patients with metastatic breast carcinoma.

*Phase 2 open-label studies:* Two studies were conducted in 53 patients previously treated with a maximum of 1 prior chemotherapeutic regimen. TAXOL was administered in these 2 trials as a 24-hour infusion at initial doses of 250 mg/m<sup>2</sup> (with G-CSF support) or 200 mg/m<sup>2</sup>. The response rates were 57% (95% CI, 37–75%) and 52% (95% CI, 32–72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL was 200 mg/m<sup>2</sup> as a 24-hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, for a response rate of 30% (95% CI, 15–50%).

*Phase 3 randomized study:* This multicenter trial was conducted in patients previously treated with 1 or 2 regimens of chemotherapy. Patients were randomized to receive TAXOL (paclitaxel) at a dose of either 175 mg/m<sup>2</sup> or 135 mg/m<sup>2</sup> given as a 3-hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% CI, 22–30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range, 3.4–18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range, 0.03–17.1 months). Median survival was 11.7 months (range, 0–18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table.

**TABLE 5**  
**EFFICACY IN BREAST CANCER AFTER FAILURE OF INITIAL**  
**CHEMOTHERAPY OR WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY**

	175/3 (n=235)		135/3 (n=236)
• <b>Response</b>			
—rate (percent)	28		22
—p-value		0.135	
• <b>Time to Progression</b>			
—median (months)	4.2		3.0
—p-value		0.027	
• <b>Survival</b>			
—median (months)	11.7		10.5
—p-value		0.321	

The adverse event profile of the patients who received single-agent TAXOL in the Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (TABLES 10 and 14) and narrative form.

### **Non-Small Cell Lung Carcinoma (NSCLC)**

In a Phase 3 open-label randomized study conducted by the ECOG, 599 patients were randomized to either TAXOL (T) 135 mg/m<sup>2</sup> as a 24-hour infusion in combination with cisplatin (c) 75 mg/m<sup>2</sup>, TAXOL (T) 250 mg/m<sup>2</sup> as a 24-hour infusion in combination with cisplatin (c) 75 mg/m<sup>2</sup> with G-CSF support, or cisplatin (c) 75 mg/m<sup>2</sup> on day 1, followed by etoposide (VP) 100 mg/m<sup>2</sup> on days 1, 2, and 3 (control).

Response rates, median time to progression, median survival, and 1-year survival rates are given in the following table. The reported p-values have not been adjusted for multiple comparisons. There were statistically significant differences favoring each of the TAXOL plus cisplatin arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either TAXOL plus cisplatin arm and the cisplatin plus etoposide arm.

**TABLE 6**  
EFFICACY PARAMETERS IN THE PHASE 3 FIRST-LINE NSCLC STUDY

	T135/24 c75 (n=198)	T250/24 c75 (n=201)	VP100 <sup>a</sup> c75 (n=200)
• <b>Response</b>			
—rate (percent)	25	23	12
—p-value <sup>b</sup>	0.001	<0.001	
• <b>Time to Progression</b>			
—median (months)	4.3	4.9	2.7
—p-value <sup>b</sup>	0.05	0.004	
• <b>Survival</b>			
—median (months)	9.3	10.0	7.4
—p-value <sup>b</sup>	0.12	0.08	
• <b>1-Year Survival</b>			
—percent of patients	36	40	32

<sup>a</sup> Etoposide (VP) 100 mg/m<sup>2</sup> was administered IV on days 1, 2, and 3.

<sup>b</sup> Compared to cisplatin/etoposide.

In the ECOG study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had 7 subscales that measured subjective assessment of treatment. Of the 7, the Lung Cancer Specific Symptoms subscale favored the TAXOL 135 mg/m<sup>2</sup>/24 hour plus cisplatin arm compared to the cisplatin/etoposide arm. For all other factors, there was no difference in the treatment groups.

The adverse event profile for patients who received TAXOL in combination with cisplatin in this study was generally consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line NSCLC study are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10 and 15**) and narrative form.

### **AIDS-Related Kaposi's Sarcoma**

Data from 2, Phase 2 open-label studies support the use of TAXOL (paclitaxel) as second-line therapy in patients with AIDS-related Kaposi's sarcoma. Fifty-nine of the 85 patients enrolled in these studies had previously received systemic therapy, including interferon alpha (32%), DaunoXome<sup>®</sup> (31%), DOXIL<sup>®</sup> (2%), and doxorubicin containing chemotherapy (42%), with 64% having received prior anthracyclines.

DaunoXome<sup>®</sup> is a registered trademark of Gilead Sciences, Inc.

DOXIL<sup>®</sup> is a registered trademark of ALZA Corporation.

Eighty-five percent of the pretreated patients had progressed on, or could not tolerate, prior systemic therapy.

In Study CA139-174, patients received TAXOL at 135 mg/m<sup>2</sup> as a 3-hour infusion every 3 weeks (intended dose intensity 45 mg/m<sup>2</sup>/week). If no dose-limiting toxicity was observed, patients were to receive 155 mg/m<sup>2</sup> and 175 mg/m<sup>2</sup> in subsequent courses. Hematopoietic growth factors were not to be used initially. In Study CA139-281, patients received TAXOL at 100 mg/m<sup>2</sup> as a 3-hour infusion every 2 weeks (intended dose intensity 50 mg/m<sup>2</sup>/week). In this study patients could be receiving hematopoietic growth factors before the start of TAXOL therapy, or this support was to be initiated as indicated; the dose of TAXOL was not increased. The dose intensity of TAXOL used in this patient population was lower than the dose intensity recommended for other solid tumors.

All patients had widespread and poor-risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease (T<sub>1</sub>), 88% had a CD4 count <200 cells/mm<sup>3</sup> (I<sub>1</sub>), and 97% had poor risk considering their systemic illness (S<sub>1</sub>).

All patients in Study CA139-174 had a Karnofsky performance status of 80 or 90 at baseline; in Study CA139-281, there were 26 (46%) patients with a Karnofsky performance status of 70 or worse at baseline.

**TABLE 7**  
EXTENT OF DISEASE AT STUDY ENTRY  
Percent of Patients

	Prior Systemic Therapy (n=59)
Visceral ± edema ± oral ± cutaneous	42
Edema or lymph nodes ± oral ± cutaneous	41
Oral ± cutaneous	10
Cutaneous only	7

Although the planned dose intensity in the 2 studies was slightly different (45 mg/m<sup>2</sup>/week in Study CA139-174 and 50 mg/m<sup>2</sup>/week in Study CA139-281), delivered dose intensity was 38 to 39 mg/m<sup>2</sup>/week in both studies, with a similar range (20–24 to 51–61).

*Efficacy:* The efficacy of TAXOL was evaluated by assessing cutaneous tumor response according to the amended ACTG criteria and by seeking evidence of clinical benefit in

patients in 6 domains of symptoms and/or conditions that are commonly related to AIDS-related Kaposi's sarcoma.

*Cutaneous Tumor Response (Amended ACTG Criteria):* The objective response rate was 59% (95% CI, 46–72%) (35 of 59 patients) in patients with prior systemic therapy. Cutaneous responses were primarily defined as flattening of more than 50% of previously raised lesions.

**TABLE 8**  
OVERALL BEST RESPONSE (AMENDED ACTG CRITERIA)  
Percent of Patients

	Prior Systemic Therapy (n=59)
Complete response	3
Partial response	56
Stable disease	29
Progression	8
Early death/toxicity	3

The median time to response was 8.1 weeks and the median duration of response measured from the first day of treatment was 10.4 months (95% CI, 7.0–11.0 months) for the patients who had previously received systemic therapy. The median time to progression was 6.2 months (95% CI, 4.6–8.7 months).

*Additional Clinical Benefit:* Most data on patient benefit were assessed retrospectively (plans for such analyses were not included in the study protocols). Nonetheless, clinical descriptions and photographs indicated clear benefit in some patients, including instances of improved pulmonary function in patients with pulmonary involvement, improved ambulation, resolution of ulcers, and decreased analgesic requirements in patients with Kaposi's sarcoma (KS) involving the feet and resolution of facial lesions and edema in patients with KS involving the face, extremities, and genitalia.

*Safety:* The adverse event profile of TAXOL administered to patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma was generally similar to that seen in the pooled analysis of data from 812 patients with solid tumors. These adverse events and adverse events from the Phase 2 second-line Kaposi's sarcoma studies are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and **16**) and narrative form. In this immunosuppressed patient population, however, a lower dose intensity of TAXOL and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors.



## INDICATIONS AND USAGE

TAXOL is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, TAXOL is indicated in combination with cisplatin.

TAXOL is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. (See **CLINICAL STUDIES: Breast Carcinoma.**)

TAXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

TAXOL, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

TAXOL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

## CONTRAINDICATIONS

TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor<sup>®</sup> EL (polyoxyethylated castor oil).

TAXOL should not be used in patients with solid tumors who have baseline neutrophil counts of  $<1500$  cells/mm<sup>3</sup> or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of  $<1000$  cells/mm<sup>3</sup>.

## WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids,

diphenhydramine, and H<sub>2</sub> antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. TAXOL should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm<sup>3</sup> (<1000 cells/mm<sup>3</sup> for patients with KS). Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm<sup>3</sup> (>1000 cells/mm<sup>3</sup> for patients with KS) and platelets recover to a level >100,000 cells/mm<sup>3</sup>.

Severe conduction abnormalities have been documented in <1% of patients during TAXOL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during TAXOL infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL.

## **Pregnancy**

TAXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m<sup>2</sup> basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m<sup>2</sup> basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If TAXOL is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## **PRECAUTIONS**

Contact of the undiluted concentrate with plasticized polyvinyl chloride (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 preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2<sup>®</sup> filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

**Drug Interactions:** In a Phase 1 trial using escalating doses of TAXOL (110–200 mg/m<sup>2</sup>) and cisplatin (50 or 75 mg/m<sup>2</sup>) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (ie, TAXOL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when TAXOL was administered following cisplatin.

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when TAXOL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. (See **CLINICAL PHARMACOLOGY**.)

Caution should also be exercised when TAXOL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. (See **CLINICAL PHARMACOLOGY**.)

Potential interactions between TAXOL, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

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IVEX-2<sup>®</sup> is the registered trademark of the Millipore Corporation.

**Hematology:** TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm<sup>3</sup>. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm<sup>3</sup> and platelets recover to a level >100,000 cells/mm<sup>3</sup>. In the case of severe neutropenia (<500 cells/mm<sup>3</sup> for 7 days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, TAXOL, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm<sup>3</sup>.

**Hypersensitivity Reactions:** Patients with a history of severe hypersensitivity reactions to products containing Cremophor<sup>®</sup> EL (eg, cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H<sub>2</sub> antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with TAXOL.

**Cardiovascular:** Hypotension, bradycardia, and hypertension have been observed during administration of TAXOL, but generally do not require treatment. Occasionally TAXOL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of TAXOL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See **WARNINGS**.) When TAXOL is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. (See **ADVERSE REACTIONS**.)

**Nervous System:** Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of TAXOL.

TAXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **PRECAUTIONS: Pediatric Use.**)

**Hepatic:** There is limited evidence that the myelotoxicity of TAXOL may be exacerbated in patients with serum total bilirubin >2 times ULN (see **CLINICAL PHARMACOLOGY**). Extreme caution should be exercised when administering TAXOL to such patients, with dose reduction as recommended in **DOSAGE AND ADMINISTRATION, TABLE 17**.

**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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** The carcinogenic potential of TAXOL (paclitaxel) has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m<sup>2</sup> basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See **WARNINGS.**)

**Pregnancy:** Pregnancy Category D. (See **WARNINGS.**)

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon 14-labeled TAXOL to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving TAXOL therapy.

**Pediatric Use:** The safety and effectiveness of TAXOL (paclitaxel) in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m<sup>2</sup> to 420 mg/m<sup>2</sup>. The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

**Geriatric Use:** Of 2228 patients who received TAXOL in 8 clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive TAXOL in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In 2 clinical studies in NSCLC, the elderly patients treated with TAXOL had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group. **TABLE 9** presents the incidences of Grade IV neutropenia and severe neuropathy in clinical studies according to age.

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

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

\* p<0.05

<sup>a</sup> TAXOL dose in mg/m<sup>2</sup>/infusion duration in hours; cisplatin doses in mg/m<sup>2</sup>.

<sup>b</sup> Peripheral neuropathy was included within the neurotoxicity category in the Intergroup First-Line Ovarian Cancer study (see TABLE 11).

<sup>c</sup> TAXOL dose in mg/m<sup>2</sup>/infusion duration in hours.

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

<sup>e</sup> Peripheral neuropathy reported as neurosensory toxicity in the Intergroup Adjuvant Breast Cancer study (see TABLE 13).

<sup>f</sup> 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<sup>2</sup> 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<sup>2</sup>) 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<sup>2</sup>) administered over 3 hours in a controlled study.



**TABLE 10**  
SUMMARY<sup>a</sup> OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS  
RECEIVING SINGLE-AGENT TAXOL

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

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> All patients received premedication.

<sup>c</sup> During the first 3 hours of infusion.

<sup>†</sup> 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<sup>a</sup> OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-  
 LINE OVARIAN CARCINOMA STUDIES**

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

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> TAXOL (T) dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>c</sup> Cyclophosphamide (C) or cisplatin (c) dose in mg/m<sup>2</sup>.

<sup>d</sup> p<0.05 by Fisher exact test.

<sup>e</sup> <130,000/mm<sup>3</sup> in the Intergroup study.

<sup>f</sup> <12 g/dL in the Intergroup study.

<sup>g</sup> All patients received premedication.

<sup>h</sup> 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.

<sup>†</sup> 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<sup>a</sup> OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

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

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> TAXOL dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>c</sup> All patients received premedication.

<sup>†</sup> 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.