Nursing Mothers
Sulfadiazine is contraindicated for use in nursing mothers because the sulfonamides cross the placenta, are excreted in breast milk and may cause kernicterus.
Because of the potential for serious adverse reactions in nursing infants from sulfadiazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. See **CONTRAINDICATIONS.**

Pediatric Use
Sulfadiazine is contraindicated in infants less than 2 months of age (except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis). See **CONTRAINDICATIONS**and **DOSAGE AND ADMINISTRATION.**

ADVERSE REACTIONS

Blood Dyscrasias
Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

Allergic Reactions
Erythema multiforme (Stevens-Johnson syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, allergic myocarditis, drug fever, and chills.

Gastrointestinal Reactions
Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

C.N.S. Reactions
Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

Renal
Crystalluria, stone formation, toxic nephrosis with oliguria and anuria; periarteritis nodosa and lupus erythematosus phenomenon have been noted.

Miscellaneous Reactions
The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

DOSAGE AND ADMINISTRATION
SYSTEMIC SULFONAMIDES ARE CONTRAINDICATED IN INFANTS UNDER 2 MONTHS OF AGE except as adjunctive therapy with pyrimethamine in the treatment of congenital toxoplasmosis.

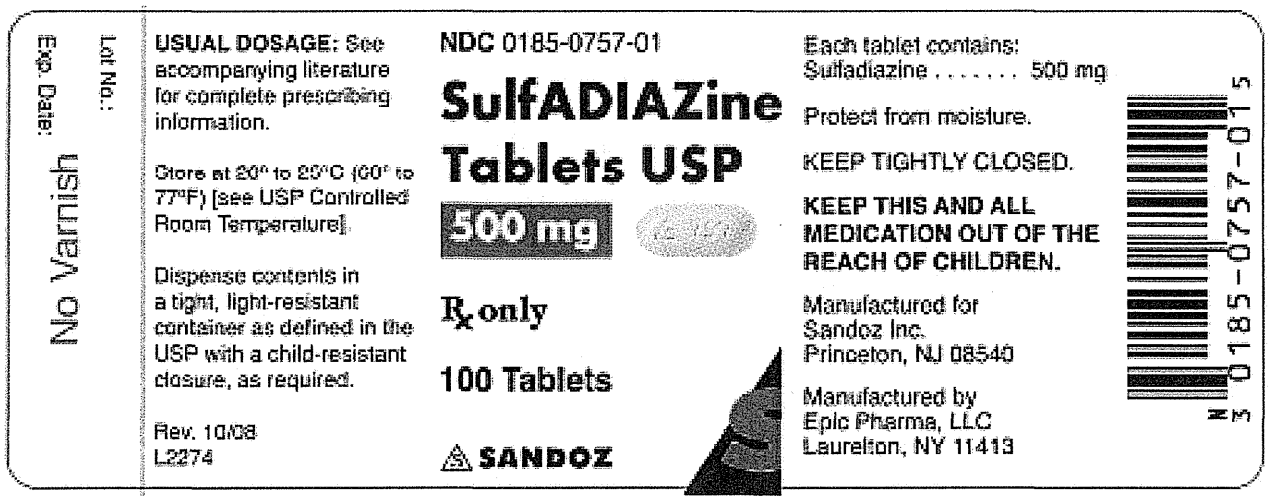
Usual Dosage for Infants over 2 Months of Age and Children
Initially, one-half the 24-hour dose. Maintenance, 150 mg/kg or 4 g/m2, divided into 4 to 6 doses, every 24 hours, with a maximum of 6 g every 24 hours. Rheumatic fever prophylaxis, under 30 kg (66 pounds), 500 mg every 24 hours; over 30 kg (66 pounds), 1 g every 24 hours.

Usual Adult Dosage
Initially, 2 to 4 g. Maintenance, 2 to 4 g, divided into 3 to 6 doses, every 24 hours.

HOW SUPPLIED
Sulfadiazine 500 mg Tablets are white, unscored, capsule-shaped tablets, imprinted *E* 757 and are available in bottles of 100 and 1000.
Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container as defined in the USP.
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Manufactured for
Sandoz Inc.
Princeton, NJ 08540
Manufactured by
Epic Pharma, LLC
Laurelton, NY 11413
OS7190

Rev. 10/08
MF0757REV10/08
MG #16918

SULFADIAZINE TABLETS USP, 500 MG X 100 TABLETS - LABEL
NDC 0185-0757-01
SulfADIAZine Tablets USP
500 mg
Rx only
100 Tablets
Sandoz



TAXOL® (paclitaxel) INJECTION

Rx only

(Patient Information Included)

WARNING

TAXOL® (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

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_2 antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

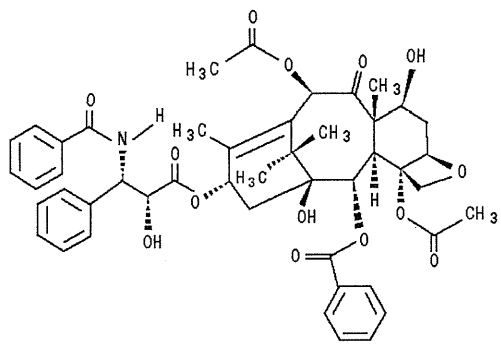
DESCRIPTION

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

*Cremophor® EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor® EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216–217° C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of TAXOL, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of TAXOL at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table.

TABLE 1
SUMMARY OF PHARMACOKINETIC PARAMETERS—MEAN VALUES

Dose (mg/m^2)	Infusion Duration (h)	N (patients)	C_{max} (ng/mL)	$AUC_{(0-\infty)}$ (ng•h/mL)	T-HALF (h)	CL_T ($L/h/m^2$)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C_{max}=Maximum plasma concentration
$AUC_{(0-\infty)}$=Area under the plasma concentration-time curve from time 0 to infinity
CL_T=Total body clearance

It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m^2 vs 175 mg/m^2) increased the C_{max} by 87%, whereas the $AUC_{(0-\infty)}$ remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and $AUC_{(0-\infty)}$ were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m^2 given by 1-hour infusions (n=15), 30 to 275 mg/m^2 given by 6-hour infusions (n=36), and 200 to 275 mg/m^2 given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of TAXOL in patients with AIDS-related Kaposi's sarcoma have not been studied.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m^2 doses of TAXOL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m^2 dose of radiolabeled TAXOL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for

the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions**.)

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤2 times upper limit of normal (ULN) administered 175 mg/m^2 was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m^2), but no observed increase in plasma exposure. (See **PRECAUTIONS: Hepatic** and **DOSAGE AND ADMINISTRATION**.) The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Ovarian Carcinoma

First-Line Data: The safety and efficacy of TAXOL followed by cisplatin in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in 2, Phase 3 multicenter, randomized, controlled trials. In an Intergroup study led by the European Organization for Research and Treatment of Cancer involving the Scandinavian Group NOCOVA, the National Cancer Institute of Canada, and the Scottish Group, 680 patients with Stage II_{B-C}, III, or IV disease (optimally or non-optimally debulked) received either TAXOL 175 mg/m^2 infused over 3 hours followed by cisplatin 75 mg/m^2 (Tc) or

cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 (Cc) for a median of 6 courses. Although the protocol allowed further therapy, only 15% received both drugs for 9 or more courses. In a study conducted by the Gynecological Oncology Group (GOG), 410 patients with Stage III or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) received either TAXOL 135 mg/m^2 infused over 24 hours followed by cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 for 6 courses.

In both studies, patients treated with TAXOL (paclitaxel) in combination with cisplatin had significantly higher response rate, longer time to progression, and longer survival time compared with standard therapy. These differences were also significant for the subset of patients in the Intergroup study with non-optimally debulked disease, although the study was not fully powered for subset analyses (**TABLES 2A** and **2B**). Kaplan-Meier survival curves for each study are shown in **FIGURES 1** and **2**.

TABLE 2A
EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

	Intergroup (non-optimally debulked subset)		**GOG-111**	
	T175/3[a] c75 (n=218)	C750[a] c75 (n=227)	T135/24[a] c75 (n=196)	C750[a] c75 (n=214)
• ***Clinical Response***[b]	(n=153)	(n=153)	(n=113)	(n=127)
—rate (percent)	58	43	62	48
—p-value[c]	0.016		0.04	
• ***Time to Progression***				
—median (months)	13.2	9.9	16.6	13.0
—p-value[c]	0.0060		0.0008	
—hazard ratio (HR)[c]	0.76		0.70	
—95% CI[c]	0.62–0.92		0.56–0.86	
• ***Survival***				
—median (months)	29.5	21.9	35.5	24.2
—p-value[c]	0.0057		0.0002	
—hazard ratio[c]	0.73		0.64	
—95% CI[c]	0.58–0.91		0.50–0.81	

[a] TAXOL dose in mg/m^2/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m^2.
[b] Among patients with measurable disease only.
[c] Unstratified for the Intergroup Study, Stratified for Study GOG-111.

TABLE 2B

EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA INTERGROUP STUDY

	T175/3[a] c75 (n=342)		C750[a] c75 (n=338)
• ***Clinical Response***[b]	(n=162)		(n=161)
—rate (percent)	59		45
—p-value[c]		0.014	
• ***Time to Progression***			
—median (months)	15.3		11.5
—p-value[c]		0.0005	
—hazard ratio[c]		0.74	
—95% CI[c]		0.63–0.88	
• ***Survival***			
—median (months)	35.6		25.9
—p-value[c]		0.0016	
—hazard ratio[c]		0.73	
—95% CI[c]		0.60–0.89	

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

[b] Among patients with measurable disease only.

[c] Unstratified.

FIGURE 1

SURVIVAL: Cc VERSUS Tc (INTERGROUP)

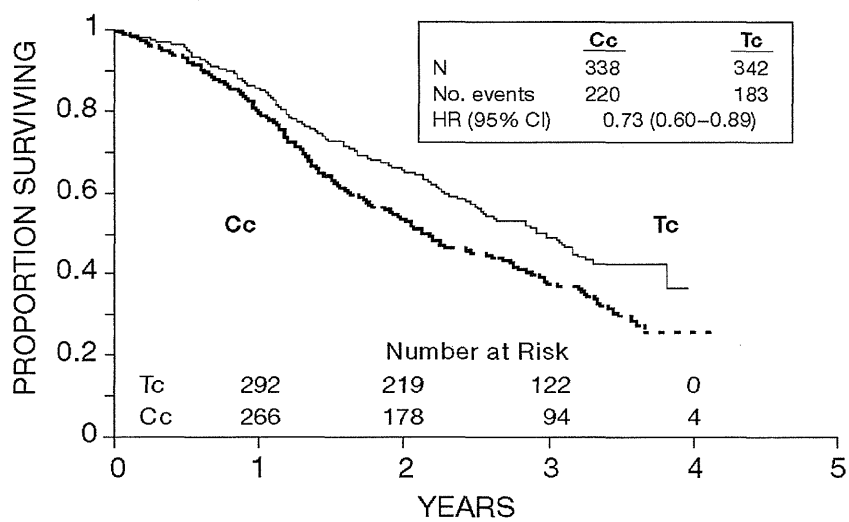
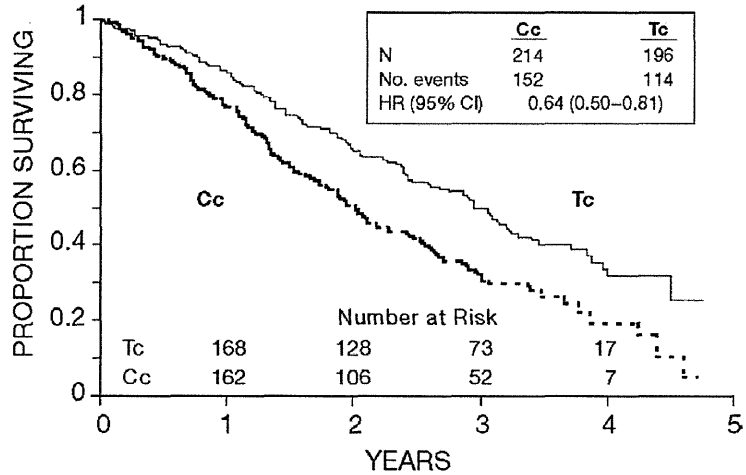


FIGURE 2
SURVIVAL: Cc VERSUS Tc (GOG-111)



The adverse event profile for patients receiving TAXOL in combination with cisplatin in these studies was qualitatively 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 ovarian carcinoma studies are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and **11**) and narrative form.

Second-Line Data: Data from 5, Phase 1 and 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of TAXOL in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these 2 studies were 22% (95% CI, 11–37%) and 30% (95% CI, 18–46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these 2 studies measured from the first day of treatment was 7.2 months (range, 3.5–15.8 months) and 7.5 months (range, 5.3–17.4 months), respectively. The median survival was 8.1 months (range, 0.2–36.7 months) and 15.9 months (range, 1.8–34.5+ months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of TAXOL (paclitaxel), administered at 2 different doses (135 or 175 mg/m^2) and schedules (3- or 24-hour infusion). The overall response rate for the 407 patients was 16.2%

(95% CI, 12.8–20.2%), with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range, 3.2–21.6 months). Median time to progression was 3.7 months (range, 0.1+ to 25.1+ months). Median survival was 11.5 months (range, 0.2 to 26.3+ months).

Response rates, median survival, and median time to progression for the 4 arms are given in the following table.

TABLE 3
EFFICACY IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

	175/3 (n=96)	175/24 (n=106)	135/3 (n=99)	135/24 (n=106)
• ***Response***				
—rate (percent)	14.6	21.7	15.2	13.2
—95% Confidence Interval	(8.5–23.6)	(14.5–31.0)	(9.0–24.1)	(7.7–21.5)
• ***Time to Progression***				
—median (months)	4.4	4.2	3.4	2.8
—95% Confidence Interval	(3.0–5.6)	(3.5–5.1)	(2.8–4.2)	(1.9–4.0)
• ***Survival***				
—median (months)	11.5	11.8	13.1	10.7
—95% Confidence Interval	(8.4–14.4)	(8.9–14.6)	(9.1–14.6)	(8.1–13.6)

Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the 2 doses (135 or 175 mg/m^2) irrespective of the schedule (3 or 24 hours) and the 2 schedules irrespective of dose. Patients receiving the 175 mg/m^2 dose had a response rate similar to that for those receiving the 135 mg/m^2 dose: 18% versus 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% versus 17% (p=0.50). Patients receiving the 175 mg/m^2 dose of TAXOL had a longer time to progression than those receiving the 135 mg/m^2 dose: median 4.2 versus 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour versus the 24-hour infusion was 4.0 months versus 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 175 mg/m^2 dose of TAXOL and 11.0 months in patients receiving the 135 mg/m^2 dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of TAXOL and 11.2 months for patients receiving the 24-hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

TAXOL remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from

completion of, a platinum-containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 and 2 clinical studies.

The adverse event profile in this 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 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and **12**) and narrative form.

The results of this randomized study support the use of TAXOL at doses of 135 to 175 mg/m^2, administered by a 3-hour intravenous infusion. The same doses administered by 24-hour infusion were more toxic. However, the study had insufficient power to determine whether a particular dose and schedule produced superior efficacy.

Breast Carcinoma

Adjuvant Therapy

A Phase 3 Intergroup study (Cancer and Leukemia Group B [CALGB], Eastern Cooperative Oncology Group [ECOG], North Central Cancer Treatment Group [NCCTG], and Southwest Oncology Group [SWOG]) randomized 3170 patients with node-positive breast carcinoma to adjuvant therapy with TAXOL or to no further chemotherapy following 4 courses of doxorubicin and cyclophosphamide (AC). This multicenter trial was conducted in women with histologically positive lymph nodes following either a mastectomy or segmental mastectomy and nodal dissections. The 3 x 2 factorial study was designed to assess the efficacy and safety of 3 different dose levels of doxorubicin (A) and to evaluate the effect of the addition of TAXOL administered following the completion of AC therapy. After stratification for the number of positive lymph nodes (1–3, 4–9, or 10+), patients were randomized to receive cyclophosphamide at a dose of 600 mg/m^2 and doxorubicin at doses of either 60 mg/m^2 (on day 1), 75 mg/m^2 (in 2 divided doses on days 1 and 2), or 90 mg/m^2 (in 2 divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for 4 courses and either TAXOL 175 mg/m^2 as a 3-hour infusion every 3 weeks for 4 additional courses or no additional chemotherapy. Patients whose tumors were positive were to receive subsequent tamoxifen treatment (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.

At the time of the current analysis, median follow-up was 30.1 months. Of the 2066 patients who were hormone receptor positive, 93% received tamoxifen. The primary analyses of disease-free survival and overall survival used multivariate Cox models, which included TAXOL administration, doxorubicin dose, number of positive lymph nodes, tumor size, menopausal status, and estrogen receptor status as factors. Based on the model for disease-free survival, patients receiving AC followed by TAXOL had a 22% reduction in the risk of disease recurrence compared to patients randomized to AC alone (Hazard Ratio [HR]=0.78, 95% CI, 0.67–0.91, p=0.0022). They also had a 26% reduction in the risk of death (HR=0.74, 95% CI, 0.60–0.92, p=0.0065). For disease-free survival and overall survival, p-values were not adjusted for interim analyses. Kaplan-Meier curves are shown in **FIGURES 3** and **4**. Increasing the dose of doxorubicin higher than 60 mg/m^2 had no effect on either disease-free survival or overall survival.

FIGURE 3
DISEASE-FREE SURVIVAL: AC VERSUS AC+T

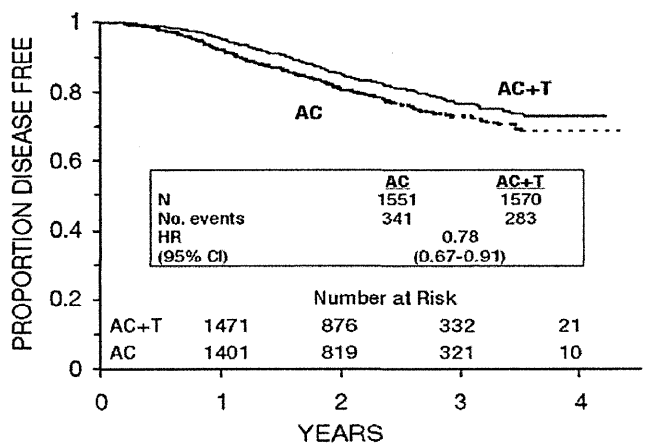
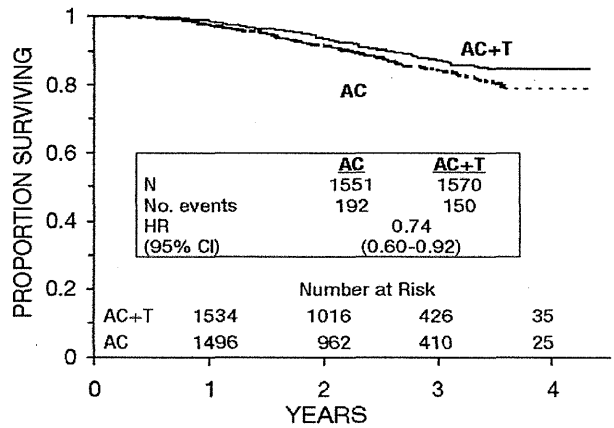


FIGURE 4
SURVIVAL: AC VERSUS AC+T



Subset analyses. Subsets defined by variables of known prognostic importance in adjuvant breast carcinoma were examined, including number of positive lymph nodes, tumor size, hormone receptor status, and menopausal status. Such analyses must be interpreted with care, as the most secure finding is the overall study result. In general, a reduction in hazard similar to the overall reduction was seen with TAXOL (paclitaxel) for both disease-free and overall survival in all of the larger subsets with one exception; patients with receptor-positive tumors had a smaller reduction in hazard (HR=0.92) for disease-free survival with TAXOL than other groups. Results of subset analyses are shown in **TABLE 4**.

TABLE 4
SUBSET ANALYSES—ADJUVANT BREAST CARCINOMA STUDY

Patient Subset	No. of Patients	Disease-Free Survival No. of Recurrences	Disease-Free Survival Hazard Ratio (95% CI)	Overall Survival No. of Deaths	Overall Survival Hazard Ratio (95% CI)
• ***No. of Positive Nodes***					
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)
• ***Tumor Size (cm)***					
≤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)
• ***Menopausal Status***					
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)
• ***Receptor Status***					
Positive[a]	2066	293	0.92 (0.73–1.16)	126	0.83 (0.59–1.18)
Negative/Unknown[b]	1055	331	0.68 (0.55–0.85)	216	0.71 (0.54–0.93)

[a] Positive for either estrogen or progesterone receptors.
[b] 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

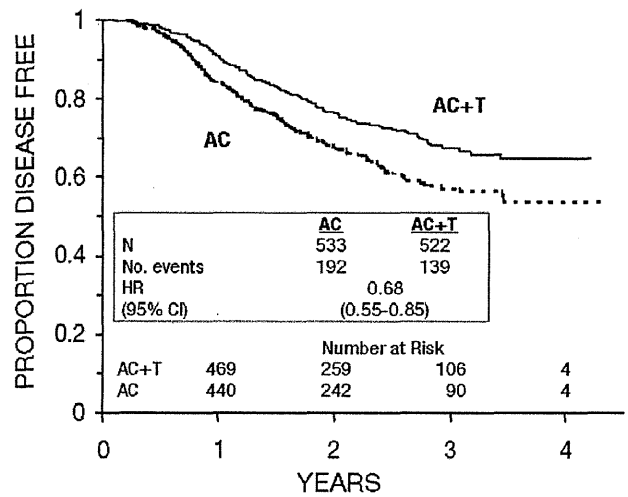


FIGURE 6
DISEASE-FREE SURVIVAL—RECEPTOR STATUS POSITIVE
AC VERSUS AC+T

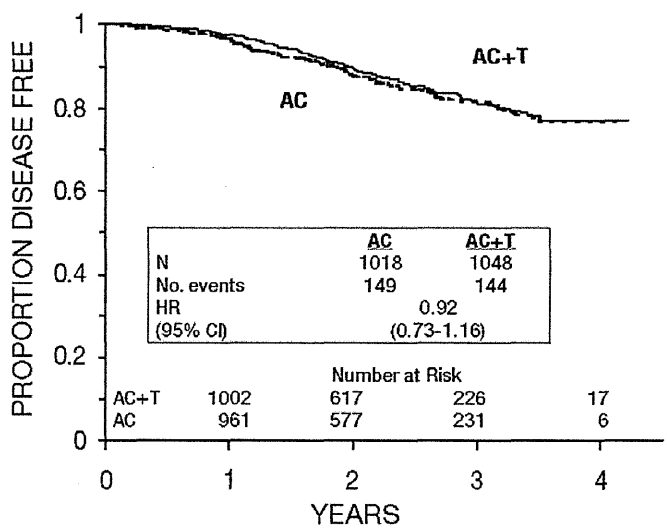


FIGURE 7
DISEASE-FREE SURVIVAL—PREMENOPAUSAL
AC VERSUS AC+T

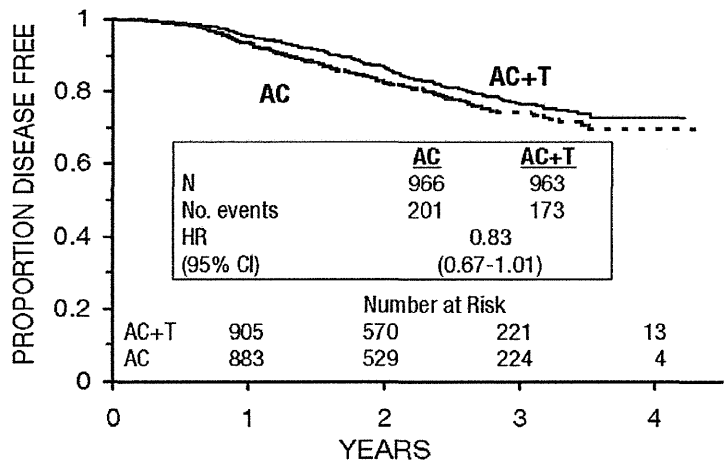
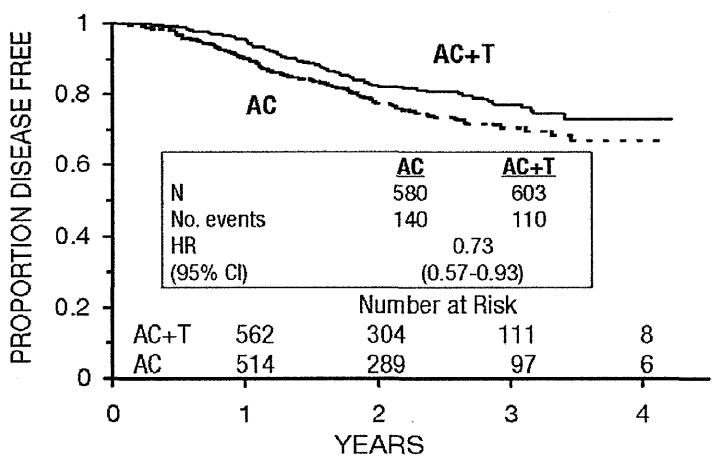


FIGURE 8
DISEASE-FREE SURVIVAL—POSTMENOPAUSAL
AC VERSUS AC+T



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^2 (with G-CSF support) or 200 mg/m^2. 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^2 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^2 or 135 mg/m^2 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)
• ***Response***			
—rate (percent)	28		22
—p-value		0.135	
• ***Time to Progression***			
—median (months)	4.2		3.0
—p-value		0.027	
• ***Survival***			
—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^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).

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[a] c75 (n=200)
• ***Response***			
—rate (percent)	25	23	12
—p-value[b]	0.001	<0.001	
• ***Time to Progression***			
—median (months)	4.3	4.9	2.7
—p-value[b]	0.05	0.004	
• ***Survival***			
—median (months)	9.3	10.0	7.4
—p-value[b]	0.12	0.08	
• ***1-Year Survival***			
—percent of patients	36	40	32

[a] Etoposide (VP) 100 mg/m^2 was administered IV on days 1, 2, and 3.
[b] 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^2/24 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® (31%), DOXIL® (2%), and doxorubicin containing chemotherapy (42%), with 64% having received prior anthracyclines.

DaunoXome® is a registered trademark of Gilead Sciences, Inc.
DOXIL® 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^2 as a 3-hour infusion every 3 weeks (intended dose intensity 45 mg/m^2/week). If no dose-limiting toxicity was observed, patients were to receive 155 mg/m^2 and 175 mg/m^2 in subsequent courses. Hematopoietic growth factors were not to be used initially. In Study CA139-281, patients received TAXOL at 100 mg/m^2 as a 3-hour infusion every 2 weeks (intended dose intensity 50 mg/m^2/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_1), 88% had a CD4 count <200 cells/mm^3 (I_1), and 97% had poor risk considering their systemic illness (S_1).

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^2/week in Study CA139-174 and 50 mg/m^2/week in Study CA139-281), delivered dose intensity was 38 to 39 mg/m^2/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