Abraxane®

(paclitaxel protein-bound particles for injectable suspension)

(albumin-bound)

For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

Oncologic Drugs Advisory Committee Meeting

SEPTEMBER 7, 2006

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AUGUST 4, 2006

EXECUTIVE SUMMARY

Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) was approved by the FDA in January 2005 under Section 505(b)(2) of the FD&C Act for the treatment of metastatic breast cancer based upon a direct comparative trial versus Taxol® (paclitaxel) Injection (Bristol Myers Squibb). Abraxane is a novel solvent-free formulation of paclitaxel in which paclitaxel is complexed only with albumin to form stable, 130 nm particles. Each 50 mL vial of Abraxane contains 100 mg of paclitaxel and approximately 900 mg of human albumin as a sterile, lyophilized cake. Each vial is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP to produce a suspension containing 5 mg/mL of paclitaxel. Reconstituted Abraxane suspension is infused at a recommended dose of 260 mg/m^2 intravenously over 30 minutes. No premedication to prevent hypersensitivity reactions is required prior to administration of Abraxane.

Abraxis has been in discussions with the FDA for several months regarding an appropriate design of a clinical study to support the approval of Abraxane for use in the adjuvant treatment of breast cancer. At a meeting between Abraxis and the Division of Oncology Drug Products on June 21, 2006, the FDA proposed that in light of a combination of facts unique to Abraxane, the advice of the Advisory Committee be sought regarding whether a randomized clinical study is required to support a labeling supplement to add the adjuvant treatment of node-positive breast cancer to the labeling for Abraxane, and if so, the trial design for the required study.

The current labeling for Abraxane (Attachment 1) describes the following indication:

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.

The following additional indication is proposed:

For the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

For the following reasons, Abraxis proposes that a randomized controlled study to demonstrate the efficacy of Abraxane compared to Taxol as adjuvant treatment for node-positive breast cancer should not be required. The unique circumstances that warrant the consideration that Abraxane be approved for adjuvant breast cancer in the absence of an efficacy trial in that setting includes the following:

- the active ingredient in Taxol and Abraxane is the same, i.e. paclitaxel
- paclitaxel (Taxol) is approved for the adjuvant treatment of breast cancer
- by eliminating solvents, Abraxane avoids any Cremophor-related toxicities, which include severe hypersensitivity reactions including anaphylactic reactions and death
- in addition to eliminating solvent-related hypersensitivity reactions, the absence of Cremophor in the Abraxane formulation permits a higher dose of paclitaxel to be administered with comparable toxicity
- a Phase 3 comparative trial of equitoxic doses of Abraxane 260 mg/m^2 and Taxol 175 mg/m^2 every 3 weeks in metastatic breast cancer, which served as the basis of approval for the NDA, Abraxane resulted in a statistically higher response rate, longer time to tumor progression and, in > 1st-line patients, longer survival; these data are directly relevant to the relative activity of the two drugs in the adjuvant setting. The response rates for Abraxane were superior to Taxol in both first and greater than first line patients.
- a second randomized comparative Phase 3 study (CA201) of Abraxane 260 mg/m^2 versus Taxol 175 mg/m^2 has been conducted in patients with metastatic breast cancer to support the approval of Abraxane in China. This 200 patient study which has recently completed accrual is being conducted at Sun Yat-Sen University Cancer Center, Guangzhou, P. R. China and 7 other centers in compliance with Good Clinical Practice (GCP) under the direction of Guan Zhong-zhen (管忠震), M.D. (Principle Investigator). An interim analysis has demonstrated results that are consistent with those in the initial Phase 3 study (CA012-0), namely a statistically significant improvement in response rate for all patients (38% vs. 21% p=0.025) and first line patients (47% vs 19% p=0.005) treated with Abraxane compared to Taxol. While only 33% of the patients at the time of this interim analysis have died or have had progression of their disease, there is a trend towards prolonged progression free survival in patients receiving Abraxane (median PFS 7.9 vs 4.5 months; HR = 0.644, p = 0.09).
- in approving new formulations of existing, active agents, Section 505(b)(2) of the FD&C Act permits the Sponsor to rely on investigations available in the approved NDA for the Reference Listed Drug, but to which it has not obtained the right of reference or use from the person by or for whom the investigations were conducted. Under 505(b)(2) the known efficacy of paclitaxel (based on the approved NDA for Taxol in the adjuvant treatment of breast cancer) should be considered in the Abraxane application for this indication.

- in a direct comparison, Abraxane and Taxol have similar paclitaxel elimination half-lives, while the Abraxane formulation demonstrated greater plasma clearance and volume of distribution. The kinetics of two of the major paclitaxel metabolites for Abraxane were similar to those reported in the literature for Taxol.

- at the dose and schedule proposed for the approval of Abraxane in the adjuvant setting, Abraxane 260 mg/m^2 every 3 weeks demonstrated superior efficacy to Taxol 175 mg/m^2 every 3 weeks in patients with metastatic breast cancer. Considering these compelling data, it would be expected that the antitumor tumor activity of Abraxane would be at least equal to that of Taxol in an earlier disease setting. However, to demonstrate this would require such a large number of patients to be infeasible.

- the resources and patient availability needed to complete a randomized adjuvant efficacy trial would be prohibitive and, even if feasible, would take over 10 years to conclude; during this time patients would continue to be exposed to the toxicities of Cremophor and would receive sub-optimal doses of paclitaxel

In light of this confluence of findings (same active ingredient, known efficacy and safety of paclitaxel in adjuvant breast cancer, approval via the 505(b)(2) regulatory pathway, demonstrated superior efficacy in breast cancer, unquestionable toxicity associated with Cremophor, and the prohibitive amount of resources required to attempt an efficacy trial in the adjuvant setting), Abraxis does not believe that a randomized safety and efficacy study should be required to extend the labeling for Abraxane to include the adjuvant treatment of node-positive breast cancer.

Abraxis is committed to conducting a randomized comparative safety study of Abraxane versus the Reference Listed Drug (RLD), Taxol, to describe the safety profile of Abraxane in this disease setting. In view of the established safety profile of Abraxane and the known toxicities associated with Cremophor, we recommend conducting this trial as a Phase 4 commitment. Given that the proposed dose of Abraxane had comparable overall tolerability compared to Taxol in the metastatic setting where a median of 6 and 5 cycles respectively were given, it is anticipated that the tolerability of 4 cycles of Abraxane would be comparable to that of 4 cycles of Taxol.

Abraxis understands the policy issues surrounding the acceptance of this proposal, and welcomes the opportunity to present its justification for this approach to the Committee.

1. ABRAXANE

Abraxane is a novel formulation of paclitaxel in which paclitaxel is complexed only with albumin to form stable, 130 nm particles. Each 50 mL vial of Abraxane contains 100 mg of paclitaxel and approximately 900 mg of human albumin as a sterile, lyophilized cake. Each vial is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP to produce a suspension containing 5 mg/mL of albumin-bound particles. Reconstituted Abraxane suspension is infused at a recommended dose of 260 mg/m^2 intravenously over 30 minutes.

Abraxane is formed using the company's proprietary nanoparticle albumin bound (*nab*™) technology that combines water insoluble compounds, such as paclitaxel, with human albumin without altering either component or forming covalent bonds. In the case of Abraxane, paclitaxel is complexed with albumin to form a 130 nm particle that is stable at high concentrations due to the negative zeta potential imparted by the albumin moiety (Figure 1). When reconstituted Abraxane suspension is injected into the bloodstream, the paclitaxel concentration decreases rapidly (mean C_{max} of paclitaxel following IV Abraxane is approximately 23 ug/ml) at which point, based upon in vitro studies using 5% albumin to simulate plasma, we believe the albumin particles disassociate into individual albumin molecules and then circulate with the paclitaxel still attached (Figure 2).

Figure 1:

Diagram to show Zeta Potential of Abraxane

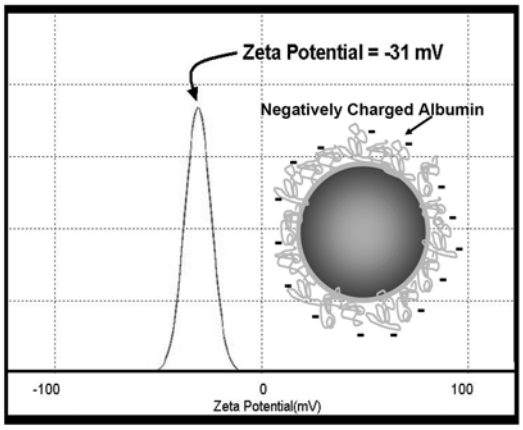
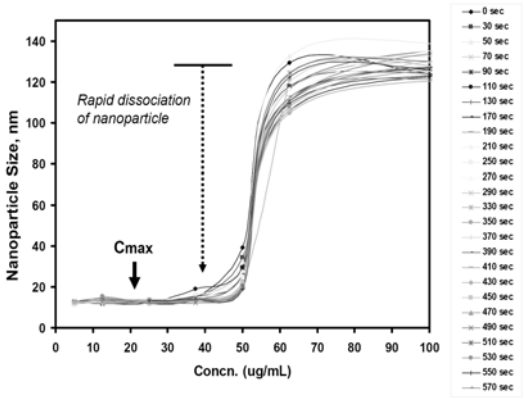


Figure 2:

Nanoparticle Release of nab-paclitaxel in 5% Albumin measured by Light Scattering



Abraxane was developed to address the unmet need for a formulation of paclitaxel that is free of the solvent Cremophor®-EL, which is known to be responsible for some of the serious side-effects and limitations of use of the approved Reference Listed Drug (RLD), Taxol (paclitaxel) Injection (Bristol Meyers Squibb Company).

Specifically, without the need for the Cremophor-EL present in the Taxol formulation, Abraxane has the following advantages:

1. Permits a higher dose of paclitaxel to be administered with comparable toxicity (260 mg/m^2 compared to 175 mg/m^2 for Taxol);
2. Increases intratumor paclitaxel concentrations by 33% (data from an equi-dose animal model);
3. Eliminates solvent-related severe hypersensitivity reactions, including anaphylactic reactions and death, permitting administration of paclitaxel over 30 minutes without premedication;
4. Eliminates need for specialized IV tubing required for Cremophor-containing products (to prevent leaching of plasticizers);
5. Results in more rapid clearance from the plasma and predictable, linear pharmacokinetics;
6. Reduces neutropenia (demonstrated clinically);
7. In the absence of Cremophor, Abraxane was well-tolerated with a median of 6 cycles administered (compared to 5 cycles with Taxol in the Phase 3 trial) and the neuropathy which occurred with Abraxane was transient.

2. ABRAXANE PRECLINICAL DATA

In its albumin-bound, nanoparticle form, paclitaxel is readily bioavailable and can be transported throughout the body and to sites of tumor using endogenous albumin pathways, processes that we have shown to be inhibited by Cremophor-EL, Tween (polysorbate) 80 and other solvents. Following administration of paclitaxel 20 mg/kg formulated as Abraxane or Taxol in an MX-1 animal model, the intratumor paclitaxel concentrations were 33% higher for Abraxane. Paclitaxel intratumor concentrations were higher even at the first time point measured (5 minutes) demonstrating the ready bioavailability of the albumin-particle based formulation (Figure 3). (Please note – tumor paclitaxel concentrations have not been measured in humans following the administration of Abraxane or Taxol).

Figure 3: Intratumor Paclitaxel Levels

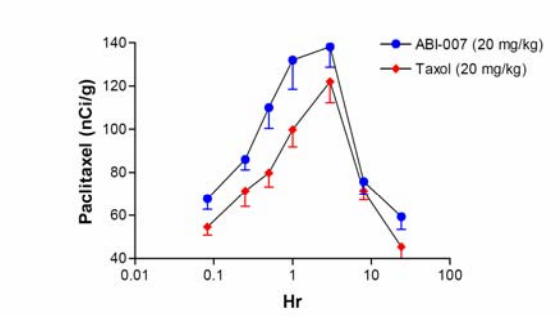


Figure 9 Intratumor Paclitaxel Levels Following Equal Doses ABI-007 and Taxol in Nude Mice Bearing MX-1 Human Breast Cancer Xenografts

Data from the 5 minute time point in the experiment represented in Figure 3 are reported in Table 1 below.

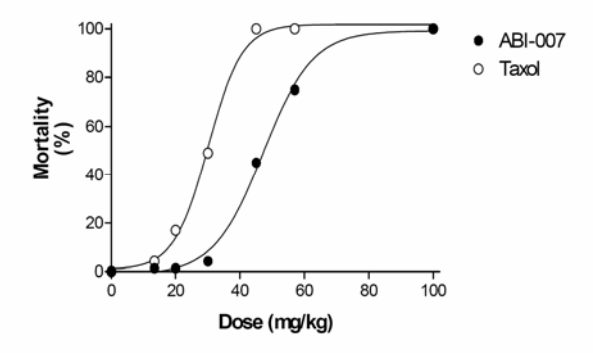
Table 1: Data from 5 Minute Time Point

Time point after drug administration	Abraxane (N=5): Tumor radioactivity nCi/g	Taxol (N=5): Tumor radioactivity nCi/g	Abraxane:Taxol, Tumor radioactivity ratio	p-value (t-test, two tailed)
5 minutes	68±11	34±20	2.0	0.01

These data show clearly that even at the earliest timepoint in the study (5 minutes), intratumor paclitaxel concentrations with Abraxane were already twice that seen for Taxol.

In the absence of solvents, the overall toxicity of paclitaxel was reduced, resulting in a 50% increase in the paclitaxel LD_{50} (47 vs 30 mg/kg) for Abraxane over Taxol in animal models (Figure 4). This observation accurately predicted the clinical maximum tolerated dose for Abraxane (300 mg/m^2 every 3 weeks compared to 175-200 mg/m^2 for Taxol). Based upon the 33% higher intratumor concentration when the same dose of paclitaxel is administered in the MX-1 tumor model combined with a 50% increase in dose, we estimate that the intratumor paclitaxel concentrations are approximately double (1.33 x 1.5 = 2.0) those achieved following standard administration of Taxol in breast cancer.

Figure 4: LD_{50} for Taxol and Abraxane



3. METABOLISM AND PHARMACOKINETICS OF ABRAXANE

Metabolism. The major metabolite of paclitaxel is 6α-hydroxypaclitaxel (Harris et al., 1994; Gianni et al., 1995; Huizing et al., 1995 & 1995a; Sparreboom et al., 1995; Sonnichsen et al., 1995; Monsarrat et al., 1998). 3'-p-hydroxypaclitaxel and 6α,3'- p-dihydroxypaclitaxel are considered to be minor metabolites, (Royer et al. 1995). The metabolism of Abraxane administered at a dose of 260 mg/m^2 was characterized in 12 patients treated with metastatic breast cancer directly assigned to the drug as a sub-study of the randomized Phase 3 trial (CA012). The whole blood metabolites of 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel were evaluated and compared to published data on the plasma metabolites for Cremophor-based paclitaxel (Table 2 and Table 3). The time of the peaks for both metabolites occurred between 0.1 and 0.3 hours after the end of the infusion for 6α-hydroxypaclitaxel and 0.25 to 0.5 hours after the end of the infusion for 3'-p-hydroxypaclitaxel. The dose adjusted AUC_{inf}'s for both metabolites were within the lower and upper limits reported by other studies for Cremophor-based paclitaxel. These parameters taken together indicate that the disposition of paclitaxel administered as either ABI-007 or the Cremophor-based preparation was similar.

Table 2: Pharmacokinetics of Metabolites: 6α-hydroxypaclitaxel

Mean Parameters[a]

Study	Dose mg/m^2	Infusion duration (hr)	C_{max} (ng/ml)	T_{max} (hr)	AUC_∞ (ng-hr/ml)	AUC_∞ /Dose	AUC_∞ Ratio Parent/Meta-bolite
CA012-0	260	0.5	591	1.11	2528	9.72	21.6[b] 7.1[c]
Gianni, et al., 1995	225	3	1105	3.2	2801	12.44	9.3
Huizing, et al., 1995	250	3	461	3.3	1361	5.34	17
Monsarrat, et al., 1998	135	3	331	3.25	1740	12.89	6.9

b where unit conversion was done, a 6α-hydroxypaclitaxel molecular weight of 869.9 was used
c mean individual paclitaxel/individual metabolite
d mean paclitaxel/ mean metabolite

Table 3: Pharmacokinetics of Metabolites: 3'-p-hydroxypaclitaxel

Mean Parameters[a]

Study	Dose mg/m^2	Infusion duration (hr)	C_{max} (ng/ml)	T_{max} (hr)	AUC_∞ (ng-hr/ml)	AUC_∞ /Dose	AUC_∞ Ratio Parent/ Metabolite
CA012-0	260	0.5	220	0.86	1075	4.13	58.9[b]
							16.7[c]
Huizing, et al., 1995	250	3	191	3.5	882	3.55	26.0
Monsarrat, et al., 1998	135	3	339	3.25	2610	19.33	4.6

a where unit conversion was done, a 3'-p-hydroxypaclitaxel molecular weight of 869.9 was used
b mean individual paclitaxel/ individual metabolite
c mean paclitaxel/mean metabolite

Where comparisons can be made the excretion pattern between studies for paclitaxel regardless of dose, formulation (ABI-007 or Cremophor-based), or infusion rate are remarkably similar (Table 4 and Table 5). These results combined with the pharmacokinetic parameters of the metabolites indicate a very similar disposition of paclitaxel that is independent whether the drug is administered as ABI-007 or the Cremophor preparation.

Table 4: Percent excreted in urine

Study	CA012-0	Walle et al., 1995	Wiernik et al., 1987	Gianni et al., 1995	Longnecker, et al., 1987	Monsarrat et al., 1998
Paclitaxel	3.9	4.5	4.3 - 6.6	2.1 – 4.4	5.9	2.7
6α-hydroxypaclitaxel	0.15	0.3				
3'-p-hydroxypaclitaxel	0.04					

Table 5: Percent excreted in feces

Study	CA012-0	Walle, et al., 1995	VanZyulen 2001
Paclitaxel	2.77	5.0	3.4
6ά-hydroxypaclitaxel	18.04		
3'-p-hydroxypaclitaxel	1.08		

Pharmacokinetics. In a subsequent study, CA008, comparative pharmacokinetic data were obtained from 24 patients who were randomly assigned to receive Abraxane or Taxol at the same dose and schedules that were used in the Phase 3 randomized trial. These data, summarized in Table 6, demonstrated a higher plasma clearance and volume of distribution for paclitaxel administered as Abraxane compared to Taxol, consistent with the preclinical data and the known paclitaxel sequestration effects of Cremophor. Consistent with the metabolic data obtained in the CA012 pharmacokinetic sub-study, the elimination half lives were similar for both formulations. Differences in the maximum concentrations and times to maximum concentration were due to differences in the doses administered (260 vs. 175 mg/m^2) and the infusion durations (30 minutes vs. 3 hours).

Table 6: CA008: Summary of Paclitaxel Pharmacokinetic Parameters for Abraxane and Taxol

	Abraxane 260 mg/m^2		Taxol 175 mg/m^2		
Parameter	**Mean**	**Range**	**Mean**	**Range**	**p-value**
Cl ($L/hr*m^2$)	21.13	8.72 – 43.41	14.76	10.20 – 28.75	0.048
Vdss ((L/m^2))	230.7	53.2 – 492.9	156.3	99.7 – 346.0	0.211
Vz (L/m^2)	663.8	296.3 – 1347.3	433.4	308.7 – 809.7	0.040
AUCinf (ng-hr/mL)	14,788.6	5981.7 – 28680.2	12,602.7	6087.1 – 17081.2	0.524
AUCinf dose corrected (ng-hr/mL)	56.84	23.04 – 114.7	71.90	34.78 – 98.00	0.049
Cmax (ng/mL)	22,968.6	4060 – 86700	3,543.3	1540 - 9380	< 0.001
Cmaxda corrected (ng/mL)	88.69	15.64 – 346.8	20.14	8.8 – 52.4	< 0.001
Tmax (hr)	0.36	0 – 0.5	2.65	1.0 – 3.5	< 0.001
λz (hr^{-1})	0.033	0.023 -0.042	0.034	0.026 – 0.040	0.477
$T_{1/2}$ (hr)	21.6	16.5 – 29.6	20.5	17.5 – 26.3	0.479
AUC%extrap (%)	2.8	1.0 – 5.0	2.8	1.4 – 6.8	0.983

Studies to determine the free and unbound fractions of paclitaxel in patients receiving Abraxane are currently underway. Based upon the literature for Taxol, it is anticipated that the free fraction for Abraxane will be higher than that of Taxol since Cremophor has been demonstrated to reduce the unbound fraction in vitro and in patients (Brouwer et al., 2000).

4. REGULATORY STRATEGY

Background on 505(b)(2)[1]
Drugs for human use may be approved under 3 primary regulations defined in the Food, Drug, and Cosmetics Act (FD&C Act). The first is Section 505(b)(1) which describes the requirements for the approval of new drugs by the submission of a full New Drug Application (NDA) which contains full reports of investigations of safety and effectiveness. Such applications are usually filed for new chemical entities to be approved for the first time in a specific indication or indications, and require extensive information on the chemistry, manufacturing, and control of the drug product, biopharmaceutics, and non-clinical and clinical safety and efficacy information.

Section 505(j) is used for the approval of generic drugs (drugs that are the same as already approved drug products) by the submission of Abbreviated New Drug Applications (ANDA). Such applications require extensive information on the chemistry, manufacturing, and controls of the drug product, and for most formulations, data to demonstrate that the proposed product is bioequivalent to the already approved reference drug (the 'Reference Listed Drug'). Non-clinical and clinical studies are usually not required for ANDAs.

A third Section of the Act that may be used for the approval of drug products is Section 505(b)(2). This Section was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) '***to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug***.' This provision expressly permits the applicant to rely on data not developed by the applicant for approval of an NDA. Specifically, applications for new formulations and dosage strengths of approved drugs are expressly covered by Section 505(b)(2). A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). Further detailed explanation of a 505(b)(2) NDA follows.

Application of Section 505(b)(2) to Abraxane for metastatic breast cancer[2]. In discussions with the FDA in February 2001 the advantages of developing a solvent-free form of paclitaxel were recognized but there was concern that the removal of Cremophor from the formulation might reduce the antitumor activity of paclitaxel. Abraxane represents a change to a previously approved drug, since the albumin-bound particle formulation of the active ingredient, paclitaxel, is substantially different from the solvent based formulation of Taxol.

Since Abraxane qualified for submission under Section 505(b)(2), the approval of the application for the change in the drug product relied on the Agency's previous finding of safety and/or effectiveness of paclitaxel for the treatment of metastatic breast cancer in the second-line setting based on information available to it in the original NDA for the reference Listed Drug (RLD) Taxol (paclitaxel) Injection (Bristol Meyers Squibb) as well as on non-clinical and clinical studies conducted by Abraxis. Therefore, it was agreed that response rate could be used as the primary endpoint to demonstrate non-inferiority to Taxol and that Abraxane could receive approval for the existing Taxol indication for metastatic breast cancer based upon a single Phase 3 trial that compared Abraxane directly to Taxol with the following caveats:

1. The response rate of Abraxane was at least 75% that of Taxol (i.e.--the lower bound of the 95% confidence interval of the ratio of the Abraxane/Taxol response rate > 0.75).
    a. If the primary endpoint of non-inferiority was met, an analysis for superiority (i.e.—lower bound > 1.0) for all patients was prospectively planned.
    b. If this endpoint was met, an analysis for superiority in first-line patients was prospectively planned.

2. Due to the non-inferiority design, the toxicity of Abraxane could not be greater than that of Taxol.

3. Recognizing that Taxol is commonly used off-label as first-line therapy, patients who had not previously received chemotherapy for metastatic disease could be treated. However, at least 100 patients in each arm had to meet the Taxol metastatic breast cancer indication (i.e. 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).

4. The previously conducted Phase 2 trials of Abraxane in metastatic breast cancer supported the results seen in the Phase 3 trial.

As discussed below, the comparative Phase 3 clinical trial to compare the safety and efficacy of Abraxane and Taxol not only confirmed that the removal of Cremophor from the formulation did not reduce the activity of paclitaxel, it demonstrated that antitumor activity was in fact enhanced. Based upon the results from the above trial, Abraxane received full approval for the treatment of metastatic breast cancer[2] on January 7, 2005.

Application of Section 505(b)(2) to Abraxane for node-positive breast cancer. Paclitaxel is approved for the adjuvant treatment of node-positive breast cancer based upon studies conducted with Taxol 175 mg/m^2 administered every 3 weeks following anthracycline therapy. In the Phase 3 trial in metastatic breast cancer, Abraxane 260 mg/m^2 was more efficacious than this dose of Taxol. Abraxis proposes to submit an NDA for Abraxane in node positive breast cancer under Section 505(b)(2) of the Act, relying on the investigations that determined the safety and effectiveness of paclitaxel (Taxol) when used in the treatment of breast cancer in the adjuvant setting. Because Abraxane was more effective than Taxol in the metastatic setting and the active agent (paclitaxel) is the same in both preparations, Abraxis proposes that further efficacy testing in the adjuvant setting is not required. Abraxis commits to conduct a randomized clinical study to describe the safety of Abraxane in this patient population and recommends conducting this trial as a Phase 4 commitment. This study would compare the toxicities of Abraxane and Taxol when administered for 4 cycles following 4 cycles of Adriamycin and Cyclophosphamide.

[1] Draft Guidance for Industry: Applications Covered by Section 505(b)(2), October 1999.
[2] Abraxane 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.

5. EFFICACY OF PACLITAXEL IN METASTATIC BREAST CANCER

5.1 Pivotal Trial Results for Abraxane in Metastatic Breast Cancer

Pivotal Trial Design. The Phase 3 trial studied 460 women with metastatic breast cancer and compared Abraxane 260 mg/m^2 to Taxol 175 mg/m^2 IV every 3 weeks. Patients could continue on treatment until disease progression, unacceptable toxicity, or withdrawal due to investigator or patient discretion.

In the Phase 3 randomized clinical trial comparing Abraxane with Taxol (Study CA012), two primary datasets measuring response rate were to be used:

1. ***Investigator Assessments***. This dataset represented the investigators' assessments of response, as coded and source-document verified on the Case Report Forms.
2. ***Independent Radiology Laboratory Assessments.*** Because the investigators could not be blinded to the treatment patients received, radiographs were submitted to an independent facility not otherwise associated with the study (World Care, Boston, MA) where the films were interpreted by radiologists who were blinded to the treatment the patient received, the investigator's response assessment and the lesions used by the investigator for his/her response assessment.

To address potential discrepancies between the two datasets, a 'reconciliation' algorithm was prospectively defined and resulted in a third, 'reconciled' data set. The reconciliation algorithm is provided in Attachment 2. In agreement with the FDA, the ***reconciled dataset*** was used to assess the primary approval endpoint of antitumor response (i.e.—the reconciled response rate).

Patient Demographics. All patients were female, 97% were Caucasian, and 83% were postmenopausal. Mean (S.D.) age was 53.2 (10.10) years; 86% of patients were < 65 years of age. Patients were enrolled at sites in Russia/Ukraine (353 patients; 77% of patients), the UK (67; 15%) and the US/Canada (40; 9%). The dominant lesion site for most patients was liver (42%) or lung (34%). Most patients had a baseline ECOG performance status of 0 (36%) or 1 (60%). At baseline, most patients had been exposed to chemotherapy (86%), anthracyclines (77%), or hormonal therapy (56%); 54% had received anthracycline treatment for metastatic disease. Most patients (59%) had received prior chemotherapy for metastatic disease; 41% had no prior chemotherapy in the metastatic setting and received ABI-007 and Taxol in this study as 1st-line therapy. The patient population for this study had poor prognostic factors in that 76% had > 3 metastatic lesions; 79% had visceral (lung, abdominal, or liver) disease; 86% had prior chemotherapy; and 59% had progressed after > 1st-line therapy.

Response Rate: The investigator assessment of overall response (*inv*ORR) was statistically significantly greater in patients receiving ABI-007 (260 mg/m^2 IV q3w) than in patients receiving Taxol (175 mg/m^2 IV q3w) for all patients, patients receiving 1st-line therapy, patients receiving > 1st-line therapy, patients with prior anthracycline therapy (adjuvant or metastatic), and patients with prior metastatic anthracycline therapy (Figures 5 and 6). Of the 76 patients in the ABI-007 group with confirmed overall responses, 74 were PR and 2 were CR; of the 42 in the Taxol group, 39 were PR and 3 were CR.

Figure 5: *inv*ORR by Line of Therapy

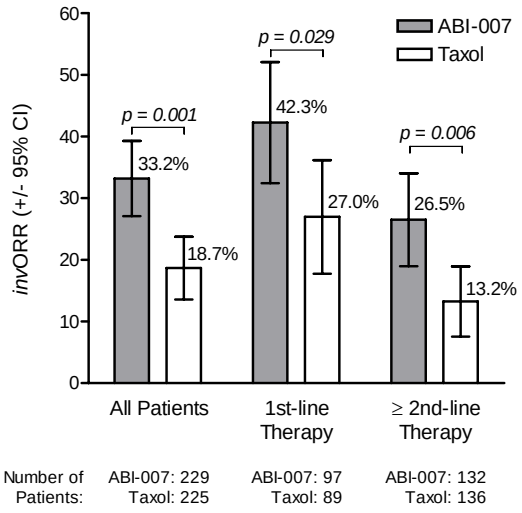
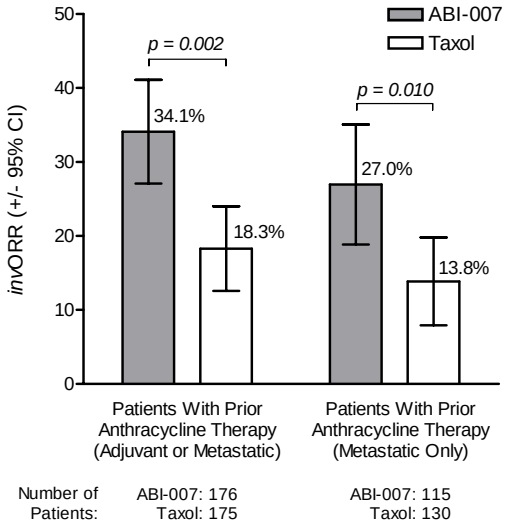


Figure 6: *inv*ORR-Patients With Prior Anthracyline Therapy



These results were confirmed using the dataset from the blinded review of tumor images by independent radiologists: response rates in the ABI-007 group were statistically significantly higher than those in the Taxol group (21.4% vs. 10.3%; P = 0.002) (Table 7). As anticipated, the blinded analysis yielded lower response rates because the central readers at the independent radiology laboratory (IRL) had only radiologic images for review and could not include lesions measurable only on physical examination. In addition, the IRL only reviewed data up to Cycle 6 while the *inv*ORR includes data for all cycles.

Table 7: Independent Radiology Laboratory Response Assessment Dataset

Category	ABI-007 (N = 229)	Taxol (N = 225)	Ratio[a] *(P-value)*[c]
IRL Response Assessment Dataset			
Patients in Dataset,[d] n	215	214	–
Patients With Overall Response, n	46	22	–
*irl*ORR, %	21.4	10.3	2.037 *(0.002*)*
Confidence Interval[b]	15.91, 26.88	6.21, 14.35	1.276, 3.252

[a] Ratio = (ABI-007 response rate) / (Taxol response rate). Ratio and 95.305% CI were adjusted for 1st line versus >1st line therapy.

[b] 95% binomial confidence interval of response rate.

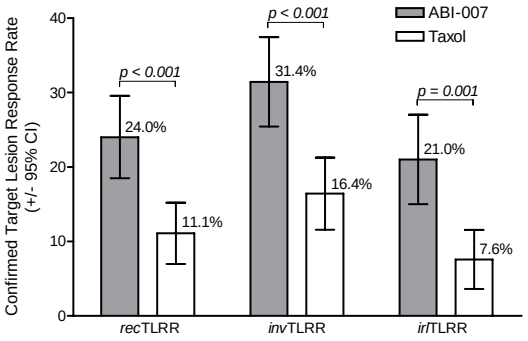
[c] P-value from CMH test stratified by 1st line vs. > 1st line therapy; * P < 0.05.

[d] The rationale for excluding patients from the IRL Response Assessment Dataset is provided in Section 9.7.1.9 CA012-0 CSR.

Source Data: Summary Tables 15.6.2, Listing 13.0, and Listing 14.0

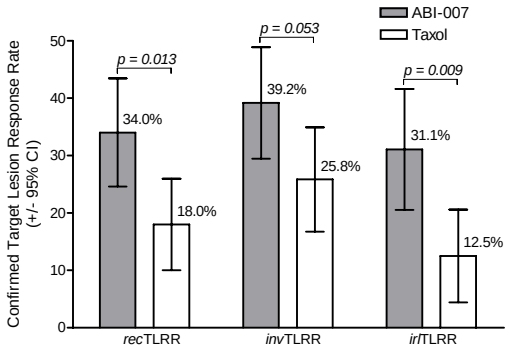
The prospectively defined analysis of the primary efficacy endpoint consisted of 3 nested tests, conducted sequentially: noninferiority (all patients), superiority (all patients), and superiority in patients receiving study drug as 1st-line therapy for metastatic disease. The *rec*TLRR was statistically significantly greater for the ABI-007 group as compared to the Taxol group for all patients (24.0% vs. 11.1%; P < 0.001) (Figure 7) and for patients receiving 1st-line therapy (34.0% vs. 18.0%; P = 0.013) (Figure 8). Regardless of the dataset used, Abraxane resulted in a statistically superior response rate compared to Taxol (Figure 9).

Figure 7: *rec*TLRR-All Patients



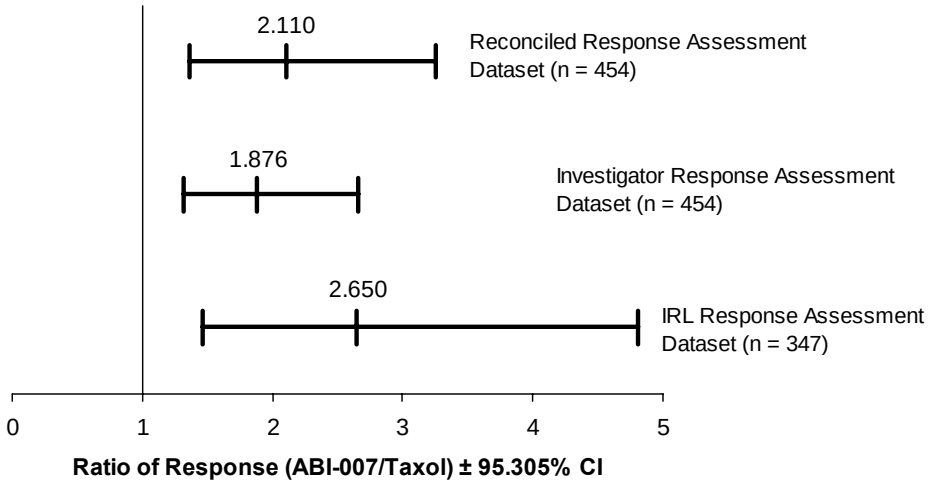
*rec*TLRR based on Reconciled Response Assessment Dataset (n = 454)
*inv*TLRR based on Investigator Response Assessment Dataset (n = 454)
*irl*TLRR based on IRL Response Assessment Dataset (n = 347)

Figure 8: *rec*TLRR-1st-Line Patients



*rec*TLRR based on Reconciled Response Assessment Dataset (n = 186)
*inv*TLRR based on Investigator Response Assessment Dataset (n = 186)
*irl*TLRR based on IRL Response Assessment Dataset (n = 138)

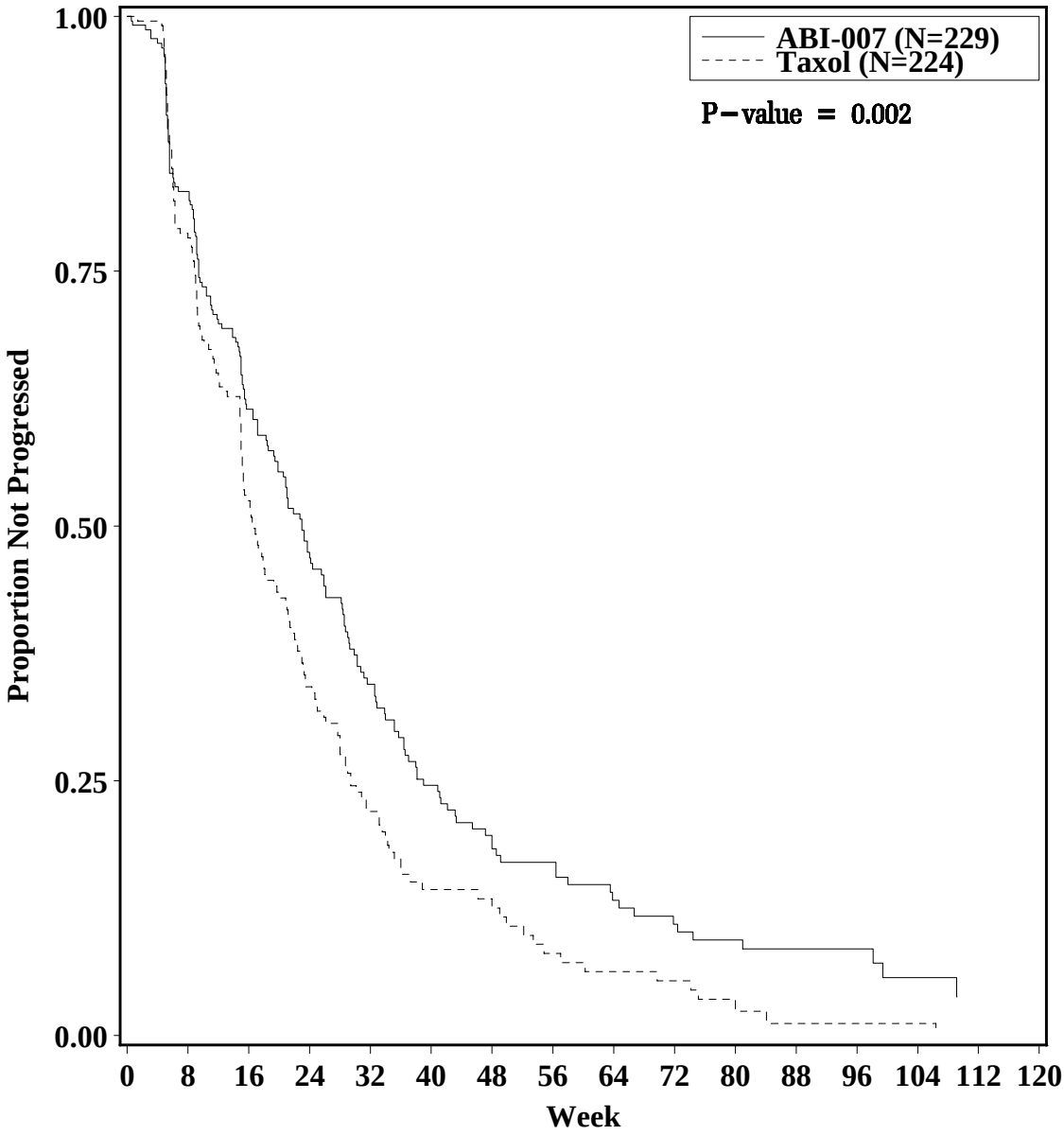
Figure 9: Ratio of Response (ABI-007/Taxol) ± 95.305% CI



The efficacy of ABI-007 was statistically significantly greater than that of Taxol among patients < 65 years old (n = 392; *inv*ORR: 34.2% vs. 18.7%; P < 0.001) and among patients with visceral (liver, lung, or abdominal) dominant site lesions (n = 358; *inv*ORR: 33.5% vs. 18.7%; P = 0.002). *inv*ORRs were also greater for ABI-007 among patients ≥ 65 years old (n = 62; 26.7% vs. 18.8%; P = 0.754) and among patients with nonvisceral dominant site lesions (n = 93; 34.0% vs. 18.6%; P = 0.074), but these results did not reach statistical significance due to the smaller number of patients in these subsets. Prognostic factors had no statistically significant effect on *inv*ORR, for all patients and within each country (US/Canada, UK and Russia/Ukraine).

Time to tumor progression. A final analysis of the data from clinical study CA012 was performed when 80% of the patients had either died or been lost to follow-up and these data were submitted to the Agency in June, 2005 as part of a post-approval obligation. Time to tumor progression for all patients was significantly longer for patients treated with Abraxane (p = 0.002, log rank) (Figure 10).

Figure 10: Time to Tumor Progression



Note: P-value from log-rank test.

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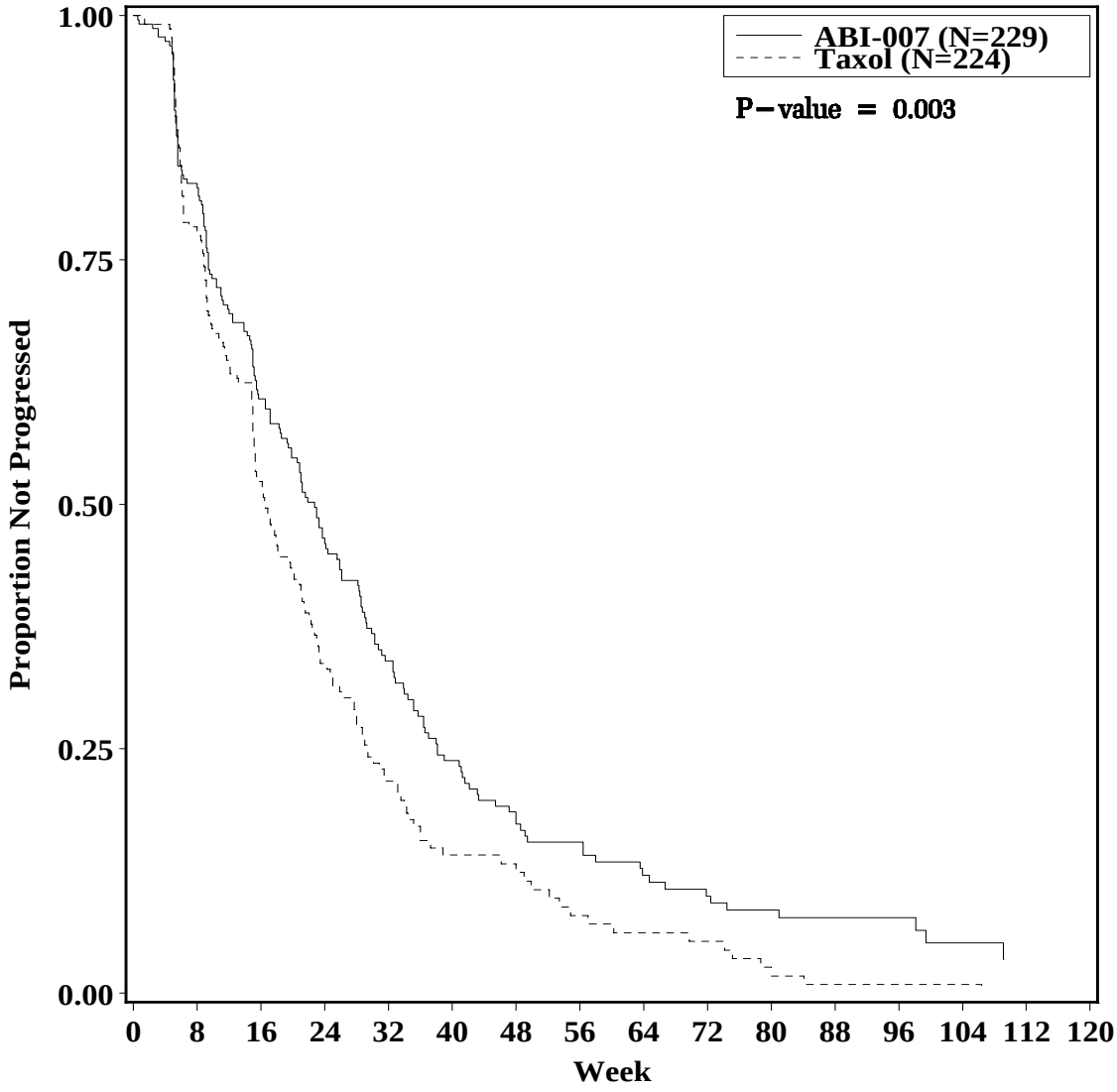
Progression Free Survival (PFS). PFS was not a pre-defined endpoint of the study. An ad-hoc analysis of PFS for all patients revealed results that were similar to TTP and are included here for completeness (Figure 11).

Figure 11: Progression-Free Survival



Note: P-value from log-rank test.

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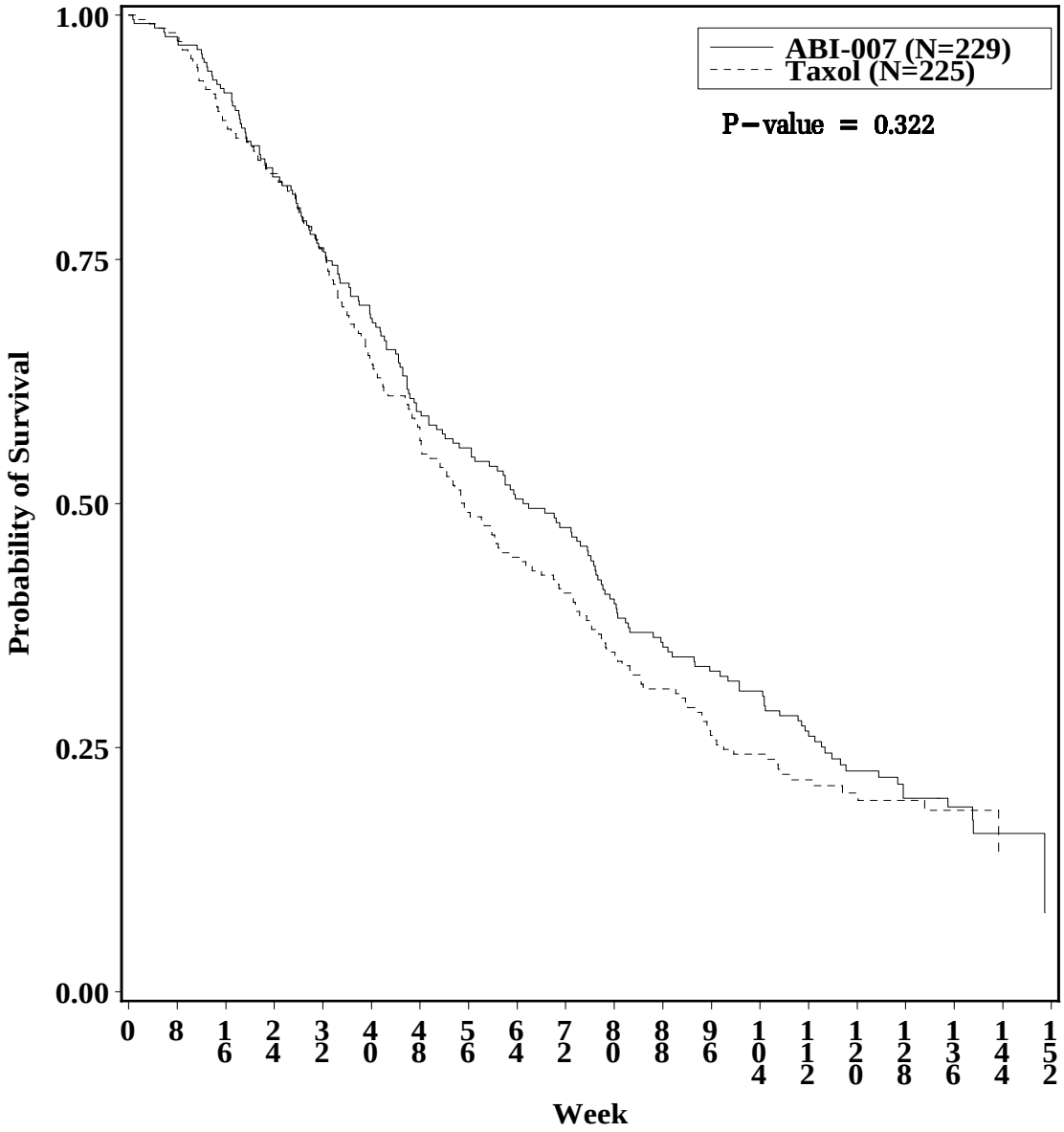
Survival. When 80% of the patients had died or were lost to follow-up, an analysis of patient survival for the two arms was performed. The median survival for patients treated with Abraxane was 10 weeks longer than for patients treated with Taxol but the survival curves were not statistically different. However, in patients who had previously received chemotherapy for metastatic disease, survival for Abraxane treated patients was significantly better than that for Taxol (median 56.4 vs. 46.7 weeks, HR .73, p =0.020 log rank) (Figure 12 and Figure 13).

Figure 12: Patient Survival Over Time for All Patients



Note: P-value from log-rank test.

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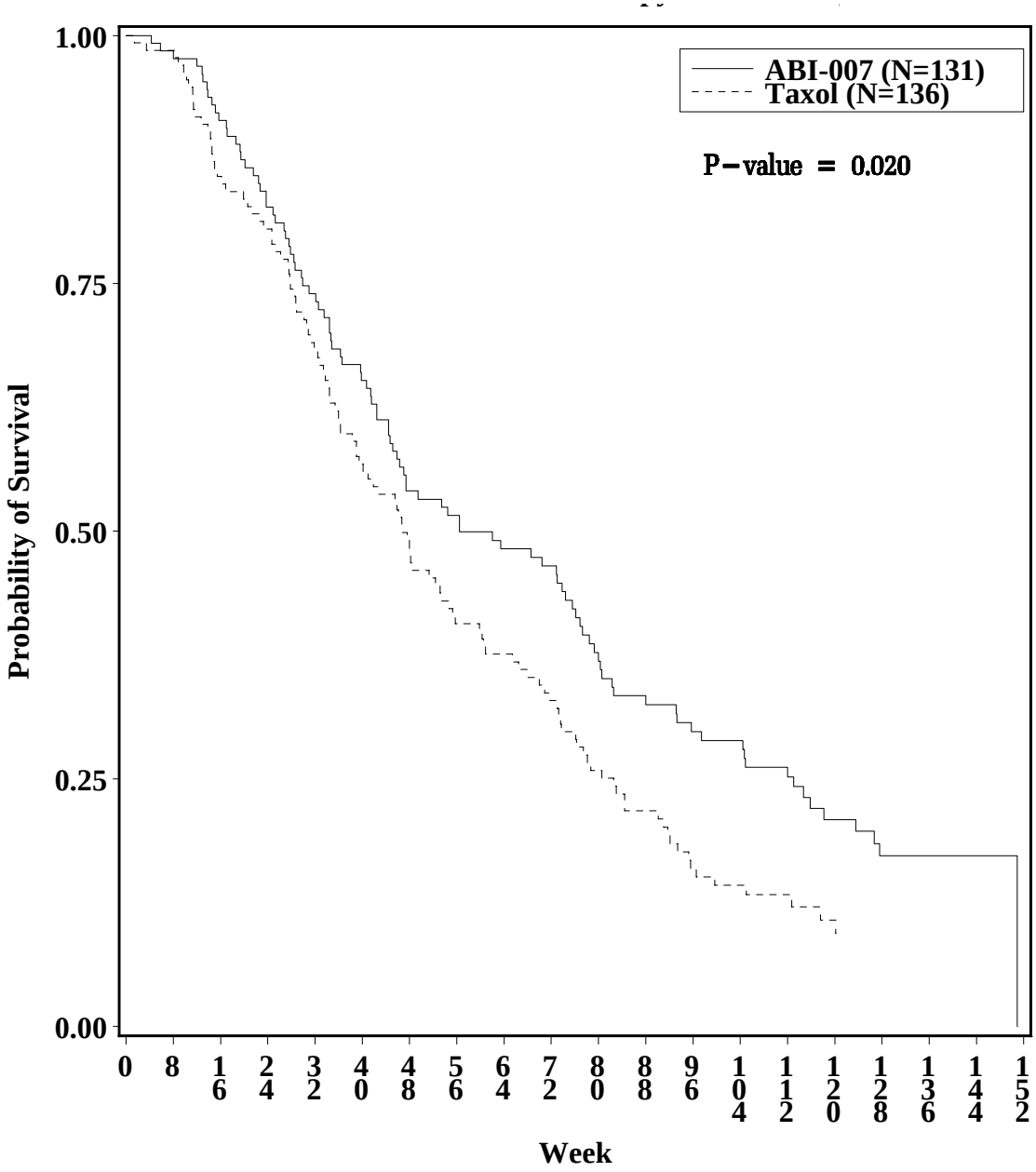
Figure 13: Patient Survival Over Time in Second-Line or Greater Line Therapy



Note: P-value from log-rank test.

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5.2 Preliminary Efficacy Data on a Phase 3 Clinical Study from China

A Phase 3 randomized trial comparing Abraxane 260 mg/m^2 with Taxol 175 mg/m^2 in 200 patients with metastatic breast cancer recently completed accrual in China. This study was approved by the Chinese regulatory authorities to support the approval of Abraxane in China. The study was conducted under GCP at 8 centers in China under the direction of the Principal Investigator Professor Guan Zhong-zhen, M.D. from the Sun Yat-Sen University Cancer Center. A recent preliminary, interim analysis of the data demonstrated that the response rate of Abraxane approximately doubled that of Taxol in all patients and that Abraxane resulted in an even greater improvement for patients receiving protocol therapy as first line treatment for their disease (Tables 8 and 9). These data appear to reproduce the results from the U.S. registrational trial (study CA012) in 460 patients. See Figures 7 and 8 on page 17 for results from study CA012.

Table 8: Confirmed Complete or Partial Overall Investigator Response Rate Per-Protocol Population

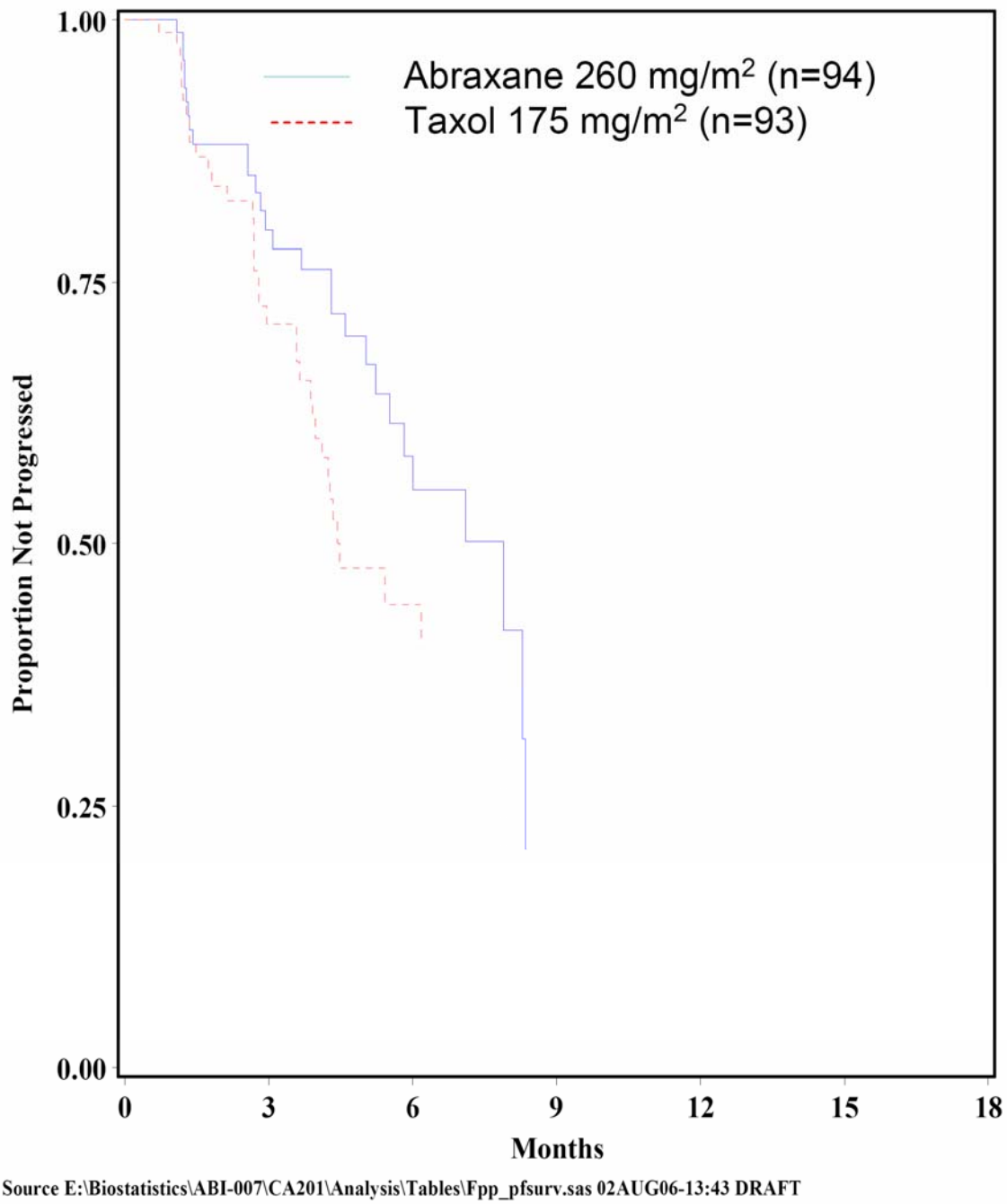
Variable Category/Statistic	Abraxane 260 mg/m^2 q3 weeks (N=94)	Taxol 175 mg/m^2 q3 weeks (N=93)	P-value
Patients Still On-Study Awaiting First Response Assessment	13	11	
Patients Evaluable for Response	81	82	
Patients with Confirmed Complete or Partial Overall Response (95% CI)	31 (38%) 27.7, 48.9	17 (21%) 12.0, 29.5	0.025*
Complete Response	1 (1%)	0	
Partial Response	30 (37%)	17 (21%)	

Table 9: Confirmed Complete or Partial Overall Investigator Response Rate Per-Protocol Population-First Line Therapy Patients

Variable Category/Statistic	Abraxane 260 mg/m^2 q3 weeks (N=55)	Taxol 175 mg/m^2 q3 weeks (N=56)	P-value
Patients Still On-Study Awaiting First Response Assessment	8	8	
Patients Evaluable for Response	47	48	
Patients with Confirmed Complete or Partial Overall Response (95% CI)	22 (47%) 32.5, 61.1	9 (19%) 7.7, 29.8	0.005*
Complete Response	0	0	
Partial Response	22 (47%)	9 (19%)	

Progression Free Survival. At the time of this interim analysis, only 30% and 37% of the patients receiving Abraxane and Taxol respectively had died or had progressive disease; the median PFS at this time was 7.9 and 4.5 months respectively, hazard ratio 0.644, p = 0.09 (Figure 14).

Figure 14: Progression Free Survival



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6. SAFETY

6.1 Toxicities of Cremophor and the Advantages of a Cremophor-free Formulation of Paclitaxel

Hypersensitivity reactions. Hypersensitivity reactions from Cremophor-EL were evident during the early clinical studies of Taxol and required steroid and antihistamine premedication and prolonged infusions to reduce, but not completely eliminate, the risk for sometimes fatal anaphylactic reactions. Since Cremophor also leached plasticizers from IV tubing, administration was further complicated by the requirement for non-PVC tubing. Because it lacks solvents, Abraxane can be administered over 30 minutes without premedication or specialized IV tubing.

Effect on paclitaxel pharmacokinetics. Subsequently, clinical pharmacokinetic studies of Taxol demonstrated a marked non-linear response between paclitaxel dose and the area under the concentration vs. time curve (AUC). For instance, increasing the dose of Taxol by 30% resulted in an increase in the AUC of 89% (Taxol Package Insert, Attachment 3). This nonlinearity has been hypothesized to be due to sequestration of paclitaxel by Cremophor micelles (Figure 15) that bound paclitaxel with high affinity. Since the volume of distribution of Cremophor approximates that of the intravascular space, paclitaxel was thus retained in the plasma. Since Cremophor micelle formation is concentration dependent, more paclitaxel sequestration is hypothesized to occur at higher Taxol doses resulting in nonlinear plasma pharmacokinetics. In contrast, the pharmacokinetics of Abraxane were linear over a wide dose range (80 to 375 mg/m^2) (Figure 16).

Figure 15: Sequestration of Paclitaxel by Cremphor Micelles

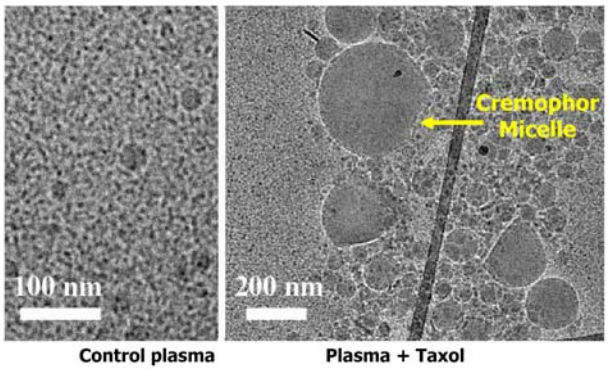
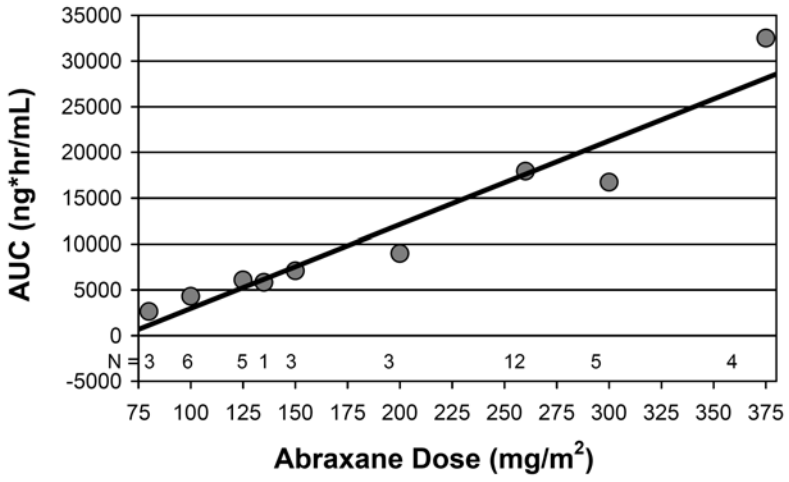


Figure 16: Linear PK of Abraxane 80-375 mg/m^2



Enhanced myelosuppression. In the Phase 3 trial (see Section 6.2) the incidence of any grade and grade 4 neutropenia was significantly reduced ($p<0.001$, CMH and Fisher's Exact respectively) in patients receiving Abraxane compared to those receiving Taxol despite a 50% increase in paclitaxel dose. The mechanism of increased myelosuppression with Taxol has not been completely defined. Currently, the most likely possible explanations are (a) Cremophor is a known inhibitor of the MDR1 gene product (pgp) and could increase the intracellular concentration of paclitaxel in hematopoietic cells (although not in tumor cells due to Cremophor's low volume of distribution) thereby accentuating the inherent myelosuppression of paclitaxel; (b) the prolonged and high vascular concentrations of paclitaxel due to Cremophor sequestration may enhance the marrow toxicity of paclitaxel; and (c) in man Cremophor and ethanol may be inherently myelosuppressive.

Prolonged neuropathy. Peripheral neuropathy from Taxol is recognized to take 'several weeks to months' to improve upon discontinuation (Taxol Package Insert, Attachment 3) and many investigators feel that severe neuropathy may never fully resolve. This was previously thought to be solely due to the anti-microtubule effects of paclitaxel. However, animals receiving injections of Cremophor and ethanol *without paclitaxel* developed axonal degeneration (Figure 17 and Figure 18) which was slow to resolve (Authier et al., 2000 and 2001).

Figure 17: Normal Axons

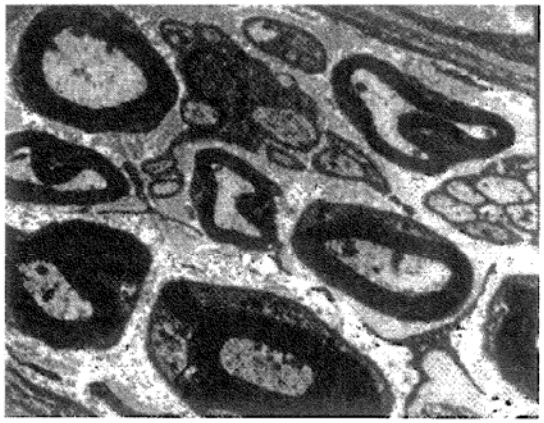


FIGURE 3 Normal axons Ultra-thin section of fine subcutaneous nerve fibers from a control (saline) rat showing several normal axons. Uranyl acetate and lead citrate (x 5000)

Figure 18: Degenerated Axons

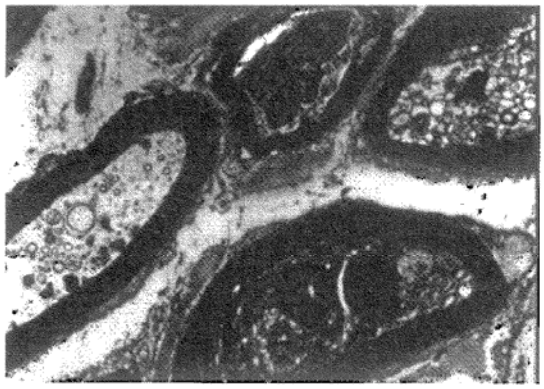


FIGURE 4 Degenerated axons Ultra-thin section of fine subcutaneous nerve fibers from a cremophor-treated rat showing several degenerated axons. Uranyl acetate and lead citrate (x 6000)

In the Phase 3 trial (see Section 6.2) the median time to improvement for Grade 3 peripheral neuropathy was 22 days for Abraxane and 79 days for Taxol. In another study of Abraxane in taxane refractory patients (n=181), study CA013, in both cohorts, patients who developed treatment-limiting sensory neuropathy typically were restarted on a reduced dose of Abraxane after a dose delay of 1 to 2 weeks.

Based upon preclinical studies demonstrating axonal degeneration from Cremophor and ethanol and the more rapid clinical improvement of Abraxane-induced neuropathy, we believe the prolonged neuropathy associated with Taxol is believed to be due to the combined effect of paclitaxel's effect on microtubules, which (based upon the Abraxane experience) appears to improve relatively quickly, and axonal degeneration from Cremophor/Ethanol which is slower to resolve. In contrast, the absence of solvents in Abraxane appears to result in a shorter-lived neuropathy, although as expected from the higher dose of paclitaxel delivered, the frequency of peripheral neuropathy was greater with Abraxane.

Thus, by eliminating the need for the Cremophor-EL and ethanol present in the Taxol formulation, Abraxane has the following advantages:

1. Permits a higher dose of paclitaxel to be administered with comparable toxicity (260 mg/m^2 compared to 175 mg/m^2 for Taxol);
2. Increases intratumor paclitaxel concentrations by 33% (data from an equi-dose animal model);
3. Eliminates solvent-related hypersensitivity reactions, including anaphylactic reactions and death, permitting administration of paclitaxel over 30 minutes without premedication;
4. Eliminates need for specialized IV tubing required for Cremophor containing products (to prevent leaching of plasticizers);
5. Results in more rapid clearance from the plasma and predictable, linear pharmacokinetics;
6. Reduces neutropenia (demonstrated clinically);
7. In the absence of Cremophor, Abraxane was well-tolerated with a median of 6 cycles administered (compared to 5 cycles with Taxol in the Phase 3 trial) and the neuropathy which occurred with Abraxane was transient.

The regulatory approval of a Cremophor-containing formulation of paclitaxel in the adjuvant treatment of breast cancer was based on the benefit of the drug outweighing the risk of severe adverse events, and particularly anaphylaxis and death caused by the Cremophor. However, the availability of a Cremophor-free formulation of paclitaxel has removed this risk factor to patients, who in the adjuvant setting, may already be disease-free.

6.2 Safety Profile of Abraxane

Safety: In the Phase 3 randomized clinical study comparing the safety and efficacy of Abraxane with Taxol, overall, the toxicity of ABI-007 was comparable to that of Taxol as assessed by patient disposition, dose delivered, discontinuations for toxicities/AEs, dose reductions, and incidence of specific toxicities/AEs. Performance status throughout the study was not statistically significantly different between the treatment groups. Compliance with the treatment regimen was high in both groups (96% in the ABI-007 group and 94% in the Taxol group received at least 90% of the protocol-specified dose) and the percentage of the planned protocol dose administered was 98% in each group (Table 10). Patients in the ABI-007 group received an average paclitaxel dose intensity 49% greater than that received by patients in the Taxol group (mean [S.D.]: 85.13 [3.118] vs. 57.02 [3.008] mg/m^2/week, respectively, Table 10). Premature discontinuations from study and dose interruptions, reductions, and delays due to toxicities/AEs occurred in fewer than 10% of patients in each group; no statistically significant differences between the groups were noted in these parameters. Dose reductions due to toxicities/AEs occurred more frequently in the ABI-007 group (7% vs. 4%), while dose interruptions and dose delays due to toxicities/AEs occurred more frequently in the Taxol group (3% vs. 6%; 3% vs. 7%, respectively).

Table 10: Cumulative Dose and Average Dose Intensity (Safety Population)

Variable	ABI-007 (N = 229)	Taxol (N = 225)
Cumulative Dose During Study (mg/m^2)		
Mean	1459.3	909.0
S.D.	787.85	494.88
Median	1560.0	875.0
min, max	260, 4680	175, 3150
Cumulative Dose During Study (mg)		
Mean	2567.6	1578.8
S.D.	1420.64	887.20
Median	2540.0	1644.0
min, max	390, 8424	10, 5760
Average Dose Intensity (mg/m^2/week)		
Mean	85.13	57.02
S.D.	3.118	3.008
Median	86.43	58.07
min, max	69.8, 92.0	31.7, 70.2
Percentage of Protocol Dose (%)		
Mean	98.2	97.8
S.D.	3.60	5.16
Median	99.7	99.5
min, max	81, 106	54, 120

Source data: Summary Table 24.2 and Listing 10.0

The most commonly reported toxicities/AEs during the study were expected for paclitaxel and included (ABI-007 group; Taxol group) alopecia (90%; 94%), sensory neuropathy (71%; 56%), fatigue (47%; 38%), neutropenia (34%; 49%), arthralgia (35%; 33%), myalgia (28%; 32%), nausea (30%; 21%), infections (24%; 20%), and diarrhea (26%; 15%).

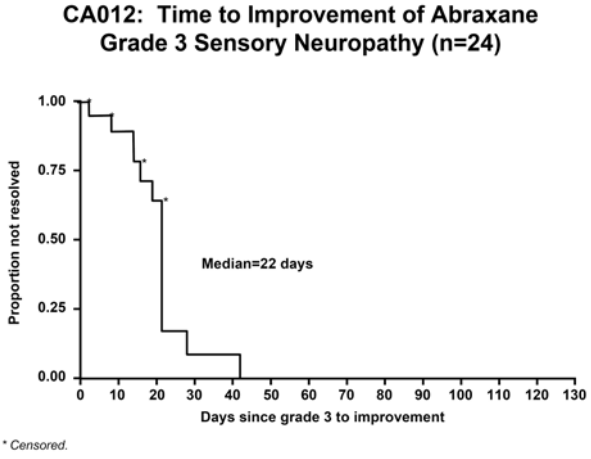
Neutropenia. Despite the higher dose, Grade 4 neutropenia occurred less frequently for the ABI-007 group ($P < 0.001$) with a higher mean neutrophil nadir (1.67 vs. 1.31 x 10^9/L, $P = 0.046$), suggesting that the Cremophor-EL may contribute to this toxicity in patients administered Taxol. Febrile neutropenia was uncommon, and there were no septic deaths in either group (Table 11).

Table 11: Neutropenia Abraxane vs. Taxol in Phase 3 Randomized Trial

ABI-007 (N = 229)					
NCI CTC Term	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neutrophils (Neutropenia)					
at any time	152 (66%)	1 (<1%)	7 (3%)	45 (20%)	24 (10%)
1st cycle only	200 (87%)	4 (2%)	4 (2%)	20 (9%)	1 (<1%)
Taxol (N = 225)					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
at any time	115 (51%)	1 (<1%)	5 (2%)	56 (25%)	48 (21%)
1st cycle only	154 (68%)	2 (<1%)	5 (2%)	45 (20%)	19 (8%)

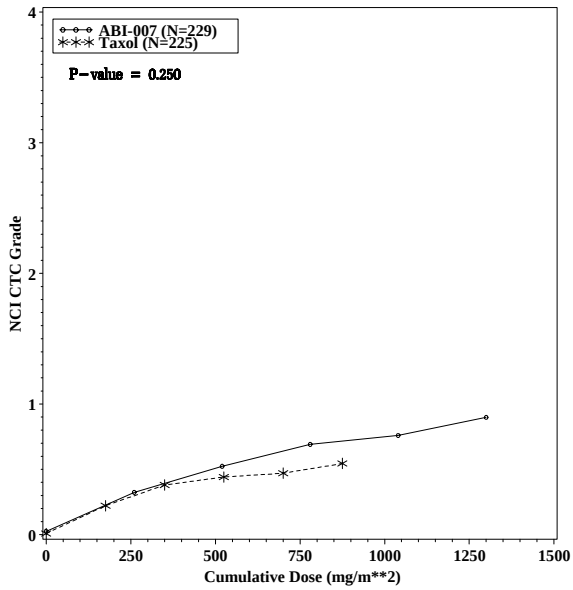
Neuropathy. As expected with a higher dose of paclitaxel with Abraxane (260 mg/m^2) compared with Taxol (175 mg/m^2), Grade 3 sensory neuropathy was 10% in the Abraxane arm versus 2% in the Taxol arm, $P < 0.001$. The Abraxane neuropathy improved rapidly and was easily managed with dose interruption and reduction—of the 14 patients who had subsequent assessments of peripheral neuropathy, 10 continued on Abraxane at a reduced dose. There were no episodes of Grade 4 sensory neuropathy in either arm. Grade 3 sensory neuropathy was transient and improved rapidly to Grade 2 or 1 by a median of 22 days in the 24 patients in the Abraxane group (Figure 19), while in the Taxol group, the median time to improvement was 79 days in 5 patients. After its first occurrence, the number of patients with persistent Grade 3 sensory neuropathy was the same (n = 4) in both arms of the study.

Figure 19:



When the physician or patient grading of peripheral neuropathy was analyzed on the basis of cumulative paclitaxel dose administered, there was no difference between the treatment groups (p>0.2) (Figure 20 and Figure 21). This finding demonstrated that the neuropathy was dependent only on total cumulative paclitaxel dose administered independent of whether paclitaxel was administered as Abraxane or as Taxol.

Figure 20: Physician Grading of Peripheral Neuropathy



Note: P-value from treatment by dose interaction effect from the following repeated measures model:
Y = Treatment Patient(Treatment) Dose Treatment*Dose.

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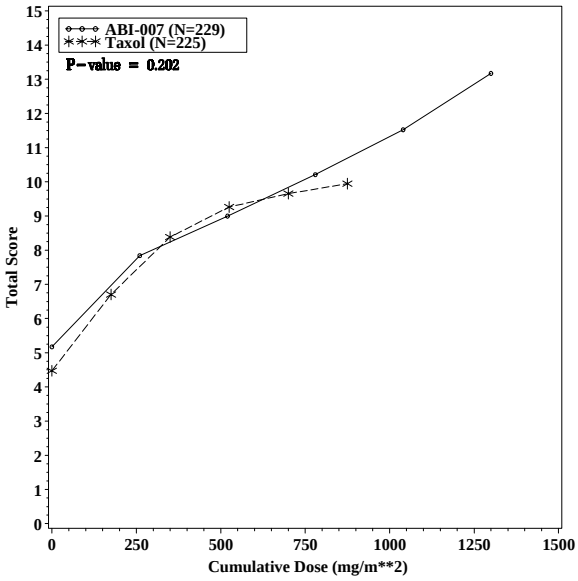
Figure 21: Patient Grading of Peripheral Neuropathy



Note: P-value from treatment by dose interaction effect from the following repeated measures model:
Y = Treatment Patient(Treatment) Dose Treatment*Dose.

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It is anticipated that the frequency of each grade of peripheral neuropathy will decrease when Abraxane is used in the adjuvant breast cancer setting since this adverse event is related to the cumulative dose administered. Four doses will be administered in the adjuvant setting, compared to a median of 6 cycles in the randomized trial in metastatic breast cancer. This is also the experience when Taxol is administered in the adjuvant breast cancer setting, with the frequency of neuropathy reported in the Taxol Package Insert (Attachment 3) being lower in patients treated in the adjuvant breast cancer setting.

To estimate what the incidence of peripheral neuropathy might be in an adjuvant setting, Abraxis determined the incidence of peripheral neuropathy in first-line patients after 4 cycles of treatment who were treated in clinical study CA012-0 (Table 12). Peripheral neuropathy was less than that described for the entire patient population (who received a median of 6 and 5 cycles of Abraxane and Taxol respectively).

Table 12: Peripheral Neuropathy After 4 Cycles of Treatment First-Line Patients

	Worst Grade Cycles 1-4				Time to improvement from Grade 3 (days) for each patient
	1	2	3	4	
Abraxane n=97	**43%**	**13%**	**5%**	**0%**	**15, 17, 22, 22, 43**
Taxol n=89	**37%**	**7%**	**2%**	**0%**	**29, 129**

6.3 Pilot Study of Abraxane in the Adjuvant Treatment of Breast Cancer

Abraxis subsequently conducted a pilot toxicity study of Abraxane in patients with node-positive breast cancer. Patients received 4 cycles of standard doxorubicin and cyclophosphamide followed by 4 cycles of Abraxane 260 mg/m^2. All chemotherapy was given in a 'dose-dense' fashion every 2 weeks. Growth factor support was routinely given with doxorubicin and cyclophosphamide (cycles 1-4) but was not used routinely with Abraxane (cycles 5-8). A total of 30 patients were entered onto the study and 29 continued on to receive Abraxane. The Abraxane portion of the treatment was delivered in a median of 6.0 weeks (range 2.0 to 7.0). In 6 patients, the delivery of Abraxane was delayed after cycle 5, possibly reflecting the withdrawal of growth factor support. Following cycles 6 and 7, Abraxane was delayed in 1 and 1 patients respectively. Two patients (7%) withdrew from the study during Abraxane therapy: 1 because of multiple toxicities (neuropathy: sensory, myalgia, and urinary incontinence), 1 at the investigator's discretion. This was comparable to the proportion of patients who did not complete 4 cycles of Taxol (8%) when administered every 3 weeks (i.e.--not dose-dense) following AC chemotherapy (Henderson et al., 2003). Grade 3 peripheral neuropathy occurred in 5 patients and improved in all 5 patients to Grade 2 or 1 at a median of 33 days.

7. ACTIVITY OF PACLITAXEL IN THE ADJUVANT TREATMENT OF BREAST CANCER

The approval of Taxol in adjuvant breast cancer was based on a trial (CALGB 9344/Intergroup 0148) that randomized 3170 node-positive patients to four 3-wk cycles of Taxol vs. no Taxol after four 3-wk cycles of doxorubicin and cyclophosphamide (AC) (Henderson et al., 2003). The primary endpoint was disease-free survival (DFS), in which an event was defined to be breast cancer recurrence or death due to any cause. That trial was designed to have 90% power for detecting a 25% decrease in hazard rate due to the addition of Taxol (equivalent to an increase in median DFS from 6 to 8 years). The target sample size was 3000 patients accrued over 3 years and followed for an additional 4 years. On the basis of a previous CALGB study in this disease, the targeted number of events after 4 years of follow-up was 1800, and there were to be interim analyses after 450, 900 and 1350 events.

CALGB 9344 accrued patients from May 1994 to April 1997. When it was published in 2003 the observed reduction in DFS events in the Taxol group was 17% (95% CI: 6% to 27%). The number of DFS events was 1054 at the time of publication. Importantly, the original target of 1800 events has still not been achieved more than nine years after the trial closed to accrual. And after more than 11 years of maximum follow-up, median DFS has still not been achieved, even in the patients not receiving Taxol.

The improved DFS in this trial in comparison with previous trials is part of a pattern that has been taking place in primary breast cancer over the last 20 years. A greater proportion of patients remains disease-free and survives longer in later trials, even conditioning on their clinical stage at randomization. There are several reasons for this trend. One is the increased use of screening mammography over the time period in question. Women whose tumors are detected mammographically fare much better than women whose tumors are detected in any other way, even after accounting for stage of disease, tumor size and nodal status (Shen et al., 2005). Another is that there have been improvements in chemotherapy, both in its delivery and in understanding of appropriate dose schedules. Still another is concomitant care, including hormonal therapy in ER/PgR-positive tumors. The above effects are well understood. There may be important effects that are not well understood. For example, there may be changes over time in the types of breast cancer that present in the clinic even though the method of detection is the same. These may be due to changes in environmental estrogen, changing eating and cultural habits, prevalence of the use of hormone replacement therapy, and other factors.

There have been additional improvements in the outcomes of breast cancer since the 1994-1997 period. For example, the U.S. Intergroup study that followed CALGB 9344 was CALGB 9741. It had essentially the same entry criteria, involved the same institutions, and it started accruing shortly after CALGB 9344 stopped accruing: namely, over the period of September 1997 to March 1999, which was an average of two and a half years after CALGB 9344. The annual rate of DFS events was 28% lower in CALGB 9741 than in CALGB 9344. Further improvements are expected because of the use of aromatase inhibitors (in post-menopausal women with hormone-sensitive disease), Herceptin in HER2 amplified tumors,

and more intensive chemotherapy regimens. Taken together these improvements are wonderful news for patients. But they make it increasingly difficult to study the benefits of therapies in this disease. Sample sizes required to achieve the same number of events have more than doubled in the last 15 years.

Moreover, refined analyses of CALGB 9344 have suggested that the benefits of Taxol are carried mostly by patients whose tumors are ER-negative (Berry et al., 2006) and HER2-positive (Hayes et al., 2006). The latter is of special concern because of the use of Herceptin. There was no Herceptin in CALGB 9344. The present and future node-positive breast cancer patients with HER2-positive tumors will be treated with Herceptin in addition to AC and a taxane and will achieve an estimated reduction in risk of DFS events that is about half that achieved by AC and a taxane alone (Piccart-Gebhart et al., 2005; Romond et al., 2005).

Taken together these considerations mean that a study attempting to show a 25% reduction in the risk of DFS events over that achieved by standard anthracycline/taxane based therapy would require several times the number of patients in CALGB 9344. However, Abraxane is not expected to substantially reduce the risk of recurrence in comparison with Taxol.

Showing non-inferiority is even more problematic. One non-inferiority standard (Rothmann et al., 2003) is to show that Abraxane preserves 50% of the benefit shown by Taxol in CALGB 9344 and NSABP B-28 (Mamounas et al., 2005). Both reductions were 17% (although the definitions of DFS were slightly different in the two trials). A randomized trial of Taxol vs. Abraxane that is designed to show that Abraxane preserves at least 50% (that is, 8.5% reduction) of the benefits of Taxol would require in excess of 30,000 patients. The patient resources for such a trial would clearly be prohibitive, as would the duration of such a study. For the reasons previously stated, Abraxis proposes that a randomized controlled study to demonstrate the efficacy of Abraxane compared to Taxol as adjuvant treatment of breast cancer should not be required.

It is interesting to note that 40% of the patients in the Phase 3 study of Abraxane versus Taxol in patients with metastatic breast cancer were treated in the first-line setting. The results showed that the efficacy of Abraxane and Taxol was greater in patients with the 'earlier' metastatic disease (first-line patients) compared to the patients treated in the second-line or greater. These data provide further evidence that Abraxane and Taxol are effective in different stages of metastatic breast cancer, and that Abraxane is more effective than Taxol even in patients who have not previously received chemotherapy for metastatic disease. There is no reason to believe that this effect will not be seen in patients treated in the adjuvant breast setting.

SUMMARY

In summary, Abraxis proposes that a randomized safety and efficacy study of Abraxane versus Taxol should not be required to support approval to amend the labeling for Abraxane to include the adjuvant treatment of node-positive breast cancer in the labeling for the following reasons:

1. The active pharmaceutical ingredient of Abraxane, paclitaxel, is identical to that of Taxol. The formulation components differ between Taxol and Abraxane in that the solvents Cremophor-EL and ethanol in Taxol are replaced with unmodified human albumin as an excipient. The FDA has determined that paclitaxel is safe and effective for the adjuvant treatment of node-positive breast cancer as evidenced by the indication in the approved package insert for Taxol (paclitaxel) Injection. Abraxis proposes to seek approval for exactly the same indication.

2. A supplemental NDA for the approval to use Abraxane for the adjuvant treatment of breast cancer may be submitted under Section 505(b)(2) of the FD&C Act since the Sponsor may rely on efficacy information available in the approved NDA for Taxol but to which it has not obtained the right of reference. Taxol was approved for the adjuvant treatment of node-positive breast cancer in 1999. One intent of Section 505(b)(2) is to '***to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug***.' This provision expressly permits the Sponsor to rely, for approval of an NDA, on data not developed by the applicant. Specifically, applications for new formulations and dosage strengths of approved drugs are expressly covered by Section 505(b)(2).

3. The FDA recognized the desirability of removing Cremophor, known to be a toxic solvent, from the Taxol formulation. The design of the Phase 3 trial of Abraxane (study CA012) was to confirm that antitumor activity was not lost by removing Cremophor from the formulation. In fact, in the comparative, randomized Phase 3 clinical study of Abraxane 260 mg/m^2 versus Taxol 175 mg/m^2 administered every 3 weeks in patients with metastatic breast cancer, patients in the Abraxane treatment group demonstrated a significant increase in tumor response rate, time to tumor progression, and, in > 1st line patients, improved survival compared to the Taxol treatment group. Abraxane and Taxol were efficacious in first-line, and greater than first-line patients, with response rates being superior in Abraxane treated patients compared to Taxol treated patients in both sub-populations. These data are directly relevant to the relative activity of the two drugs in the adjuvant setting. Preliminary efficacy data from a Phase 3 study conducted in China (CA201) in accordance with GCP confirm the results from study CA012.

4. The safety profile for Abraxane was not worse than that for Taxol despite the 49% higher paclitaxel dose delivered, and steroid premedication was not required with Abraxane. The doses per cycle for Abraxane and Taxol that were used in this trial are the same that would be used in the adjuvant setting. However, the lower cumulative dose to be used in

the adjuvant setting than used in the treatment of metastatic breast cancer would be expected to increase tolerance, consistent with the experience with Taxol.

5. The setting of advanced breast cancer, in which Abraxane demonstrated superior response rate and time to tumor progression compared to Taxol, is closely related to early stage breast cancer. Considering these compelling data, it would be expected that the antitumor tumor activity of Abraxane would be at least equal to that of Taxol in an earlier disease setting. However, to demonstrate this would require such a large number of patients to be infeasible.

6. The pharmacokinetics of paclitaxel administered as Abraxane, or Taxol show similar metabolism and elimination of half lives. As would be predicted due to sequestration of paclitaxel in Cremophor micelles following Taxol administration, the volume of distribution and plasma clearance of paclitaxel from Abraxane are greater than for Taxol. In contrast to Taxol, the pharmacokinetics of paclitaxel are linear with Abraxane.

7. It is not feasible to conduct a randomized comparative Phase 3 clinical study to compare the efficacy of Abraxane and Taxol in the adjuvant treatment of breast cancer because of the large patient numbers required (16,000 to 30,000 depending on the assumptions used) and the time required to conduct such as study (in excess of 10 years). The conduct of such a lengthy study would mean that patients would continue to be exposed to Cremophor-related toxicities, which include severe hypersensitivity reactions including anaphylactic reactions and death.

In light of this confluence of findings (same active ingredient, known efficacy and safety of paclitaxel in adjuvant breast cancer, approval via the 505(b)(2) regulatory pathway, demonstrated superior efficacy in breast cancer, unquestionable toxicity associated with Cremophor, and the prohibitive amount of resources required to attempt an efficacy trial in the adjuvant setting), Abraxis does not believe that a randomized safety and efficacy study should be required to extend the labeling for Abraxane to include the adjuvant treatment of node-positive breast cancer.

ATTACHMENTS

Attachment 1: Abraxane Package Insert

ABRAXIS ONCOLOGY

451031/Issued: January 2005

Abraxane™ for Injectable Suspension

Rx only

(paclitaxel protein-bound particles for injectable suspension)
(albumin-bound)

(Patient Information Enclosed)

WARNING

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) 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.

ABRAXANE therapy should not be administered to patients with metastatic breast cancer who have baseline neutrophil counts of less than 1,500 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 ABRAXANE.

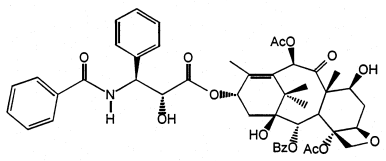
Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

DESCRIPTION:

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents.

The active agent in ABRAXANE is paclitaxel, a natural product with antitumor activity. Paclitaxel is obtained from *Taxus media*. 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 fomula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C.

CLINICAL PHARMACOLOGY:

Mechanism of Action

ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is an 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. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Human Pharmacokinetics

The pharmacokinetics of total paclitaxel following 30- and 180-minute infusions of ABRAXANE at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. Following intravenous administration of ABRAXANE, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was about 27 hours.

The drug exposure (AUCs) was dose proportional over 80 to 375 mg/m^2 and the pharmacokinetics of paclitaxel for ABRAXANE were independent of the duration of administration. At the recommended ABRAXANE clinical dose, 260 mg/m^2, the mean maximum concentration of paclitaxel, which occurred at the end of the infusion, was 18,741 ng/mL. The mean total clearance was 15 L/hr/m^2. The mean volume of distribution was 632 L/m^2; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetic data of 260 mg/m^2 ABRAXANE administered over 30 minutes was compared to the pharmacokinetics of 175 mg/m^2 paclitaxel injection over 3 hours. The clearance of ABRAXANE was larger (43%) than for the clearance of paclitaxel injection and the volume of distribution of ABRAXANE was also higher (53%). Differences in C_{max} and C_{max} corrected for dose reflected differences in total dose and rate of infusion. There were no differences in terminal half-lives.

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 a 30-minute infusion of 260 mg/m^2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by CYP2C8; and to two 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 effect of renal or hepatic dysfunction on the disposition of ABRAXANE has not been investigated.

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

CLINICAL STUDIES:

Metastatic Breast Carcinoma

Data from 106 patients accrued in two single arm open label studies and from 460 patients enrolled in a randomized comparative study were available to support the use of ABRAXANE in metastatic breast cancer.

Single Arm Open Label Studies

In one study, ABRAXANE was administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilized a dose of 300 mg/m^2 as a 30 minute infusion in 63 patients with metastatic breast cancer. Cycles were administered at 3 week intervals. Objective responses were observed in both studies.

Randomized Comparative Study

This multicenter trial was conducted in 460 patients with metastatic breast cancer. Patients were randomized to receive ABRAXANE at a dose of 260 mg/m^2 given as a 30-minute infusion, or paclitaxel injection at 175 mg/m^2 given as a 3-hour infusion. Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting, 40% in the metastatic setting and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study drug as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

In this trial, patients in the ABRAXANE treatment arm had a statistically significantly higher reconciled target lesion response rate (the trial primary endpoint) of 21.5% (95% CI: 16.2% to 26.7%), compared to 11.1% (95% CI: 6.9% to 15.1%) for patients in the paclitaxel injection treatment arm. See Table 1.

Table 1: Efficacy Results from Randomized Trial

		ABRAXANE 260 mg/m²	Paclitaxel Injection 175 mg/m²
Reconciled Target Lesion Response Rate (primary endpoint)[a]			
All randomized patients	Response Rate [95% CI]	50/233 (21.5%) [16.19% to 26.73%]	25/227 (11.1%) [6.94% to 15.09%]
	P-value[b]	0.003	
Patients who had failed combination chemotherapy or relapsed within 6 months of adjuvant chemotherapy[c]	Response Rate [95% CI]	20/129 (15.5%) [9.26% to 21.75%]	12/143 (8.4%) [3.85% to 12.94%]

[a] Reconciled Target Lesion Response Rate (TLRR) was the prospectively defined protocol specific endpoint, based on independent radiologic assessment of tumor responses reconciled with investigator responses (which also included clinical information) for the first 6 cycles of therapy. The reconciled TLRR was lower than the investigator Reported Response Rates, which are based on all cycles of therapy.
[b] From Cochran-Mantel-Haenszel test stratified by 1st line vs. > 1st line therapy.
[c] Prior therapy should have included an anthracycline unless clinically contraindicated.

INDICATION:
ABRAXANE™ for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) 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.

CONTRAINDICATIONS:
ABRAXANE should not be used in patients who have baseline neutrophil counts of < 1,500 cells/mm³.

WARNINGS:
Bone marrow suppression (primarily neutropenia) is dose dependent and a dose limiting toxicity. ABRAXANE should not be administered to patients with baseline neutrophil counts of < 1,500 cells/mm³. Frequent monitoring of blood counts should be instituted during ABRAXANE treatment. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³.

The use of ABRAXANE has not been studied in patients with hepatic or renal dysfunction. In the randomized controlled trial, patients were excluded for baseline serum bilirubin >1.5 mg/dL or baseline serum creatinine >2 mg/dL.

Pregnancy – Teratogenic Effects: Pregnancy Category D
ABRAXANE can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia, and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women using ABRAXANE. If this drug 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 while receiving treatment with ABRAXANE.

Use in Males
Men should be advised to not father a child while receiving treatment with ABRAXANE (see **PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility*** for discussion of effects of ABRAXANE exposure on male fertility and embryonic viability).

Albumin (Human)
ABRAXANE contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS:
Drug Interactions
No drug interaction studies have been conducted with ABRAXANE.

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering ABRAXANE (paclitaxel protein-bound particles for injectable suspension) concomitantly with known substrates or inhibitors of CYP2C8 and CYP3A4 (see **CLINICAL PHARMACOLOGY**).

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

Hematology
ABRAXANE therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving ABRAXANE. Patients should not be retreated with subsequent cycles of ABRAXANE until neutrophils recover to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of ABRAXANE therapy, a dose reduction for subsequent courses of therapy is recommended (see **DOSAGE AND ADMINISTRATION**).

Nervous System
Sensory neuropathy occurs frequently with ABRAXANE. The occurrence of grade 1 or 2 sensory neuropathy does not generally require dose modification. If grade 3 sensory neuropathy develops, treatment should be withheld until resolution to grade 1 or 2 followed by a dose reduction for all subsequent courses of ABRAXANE (see **DOSAGE AND ADMINISTRATION**).

Injection Site Reaction
Injection site reactions occur infrequently with ABRAXANE and were mild in the randomized clinical trial. 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 ABRAXANE 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). ABRAXANE was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel protein-bound particles to male rats at 42 mg/m² on a weekly basis (approximately 16% of the daily maximum recommended human exposure on a mg/m² basis) for 11 weeks prior to mating with untreated female rats resulted in significantly reduced fertility accompanied by decreased pregnancy rates and increased loss of embryos in mated females. A low incidence of skeletal and soft tissue fetal anomalies was also observed at doses of 3 and 12 mg/m²/week in this study (approximately 1 to 5% of the daily maximum recommended human exposure on a mg/m² basis). Testicular atrophy/degeneration has also been observed in single-dose toxicology studies in rodents administered paclitaxel protein-bound particles at 54 mg/m² and dogs administered 175 mg/m² (see **WARNINGS**).

Pregnancy – Teratogenic Effects: Pregnancy Category D
(See **WARNINGS** section).

Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel 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 ABRAXANE therapy.

Pediatric Use
The safety and effectiveness of ABRAXANE in pediatric patients have not been evaluated.

Geriatric Use
Of the 229 patients in the randomized study who received ABRAXANE, 11% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among elderly patients who received ABRAXANE.

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

ADVERSE REACTIONS:
The following table shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent ABRAXANE or paclitaxel injection for the treatment of metastatic breast cancer.

Table 2: Frequency[a] of Important Treatment Emergent Adverse Events in the Randomized Study on an Every-3-Weeks Schedule

	Percent of Patients	
	ABRAXANE 260/30min[b] (n=229)	Paclitaxel Injection 175/3h[c,d] (n=225)
Bone Marrow		
Neutropenia		
< 2.0 x 10⁹/L	80	82
< 0.5 x 10⁹/L	9	22
Thrombocytopenia		
< 100 x 10⁹/L	2	3
< 50 x 10⁹/L	<1	1
Anemia		
< 11 g/L	33	25
< 8 g/L	1	<1
Infections	24	20
Febrile Neutropenia	2	1
Bleeding	2	2
Hypersensitivity Reaction[e]		
All	4	12
Severe[f]	0	2
Cardiovascular		
Vital Sign Changes[g]		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events[f]	3	4
Abnormal ECG		
All patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	6	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms[f]	10	2
Myalgia/Arthralgia		
Any Symptoms	44	49
Severe Symptoms[f]	8	4
Asthenia		
Any Symptoms	47	38
Severe Symptoms[f]	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms[f]	0	1
Gastrointestinal		
Nausea		
Any symptoms	30	21
Severe symptoms[f]	3	<1
Vomiting		
Any symptoms	18	9
Severe Symptoms[f]	4	1
Diarrhea		
Any Symptoms	26	15
Severe Symptoms[f]	<1	1
Mucositis		
Any Symptoms	7	7
Severe Symptoms[f]	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	1	1

[a] Based on worst grade
[b] ABRAXANE dose in mg/m²/duration in minutes
[c] paclitaxel injection dose in mg/m²/duration in hours
[d] paclitaxel injection pts received premedication
[e] Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.
[f] Severe events are defined as at least grade 3 toxicity
[g] During study drug dosing.

Myelosuppression and sensory neuropathy were dose related.

Adverse Event Experiences by Body System
Unless otherwise noted, the following discussion refers to the primary safety database of 229 patients with metastatic breast cancer treated with single-agent ABRAXANE in the randomized

controlled trial. The frequency and severity of important adverse events for the study are presented above in tabular form. In some instances, rare severe events observed with paclitaxel injection may be expected to occur with ABRAXANE.

Hematologic
Neutropenia, the most important hematologic toxicity, was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2.

In the randomized metastatic breast cancer study, infectious episodes were reported in 24% of the patients treated with a dose of 260 mg/m^2 given as a 30-minute infusion. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications. Febrile neutropenia was reported in 2% of patients in the ABRAXANE arm and 1% of patients in the paclitaxel injection arm.

Thrombocytopenia was uncommon. In the randomized metastatic breast cancer study, bleeding episodes were reported in 2% of the patients in each treatment arm.

Anemia (Hb <11 g/dL) was observed in 33% of patients treated with ABRAXANE in the randomized trial and was severe (Hb <8 g/dL) in 1% of the cases. Among all patients with normal baseline hemoglobin, 31% became anemic on study and 1% had severe anemia.

Hypersensitivity Reactions (HSRs)
In the randomized controlled metastatic breast cancer study, Grade 1 or 2 HSRs occurred on the day of ABRAXANE administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of ABRAXANE in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
Hypotension, during the 30-minute infusion, occurred in 5% of patients in the randomized metastatic breast cancer trial. Bradycardia, during the 30-minute infusion, occurred in <1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent ABRAXANE occurred in approximately 3% of patients in the randomized trial. These events included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported rarely.

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 60% of patients in the metastatic breast cancer randomized trial. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory
Reports of dyspnea (12%) and cough (6%) were reported after treatment with ABRAXANE in the randomized trial. Rare reports (<1%) of pneumothorax were reported after treatment with ABRAXANE. Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of radiation pneumonitis have been received in paclitaxel injection patients receiving concurrent radiotherapy. There is no experience with the use of ABRAXANE with concurrent radiotherapy.

Neurologic
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 ABRAXANE. In the randomized trial, sensory neuropathy was observed in 71% of patients (10% severe) in the ABRAXANE arm and in 56% of patients (2% severe) in the paclitaxel injection arm. The frequency of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of ABRAXANE discontinuation in 7/229 (3%) patients in the randomized trial. In the randomized comparative study, 24 patients (10%) treated with ABRAXANE developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of ABRAXANE and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No incidences of grade 4 sensory neuropathies were reported in the clinical trial. Only one incident of motor neuropathy (grade 1) was observed in either arm of the controlled trial.

Reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel injection safety.

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with ABRAXANE in single arm and randomized trials and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients in a single arm study who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection have suggested persistent optic nerve damage.

Arthralgia/Myalgia
Forty-four percent of patients treated in the randomized trial experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after ABRAXANE administration, and resolved within a few days.

Hepatic
Among patients with normal baseline liver function treated with ABRAXANE in the randomized trial, 7%, 36%, and 39% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with ABRAXANE and 10% of patients treated with paclitaxel injection in the randomized trial.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment.

Renal
Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Gastrointestinal (GI)
Nausea/vomiting, diarrhea, and mucositis were reported by 33%, 27%, and 7% of ABRAXANE treated patients in the randomized trial.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
Injection site reactions have occurred infrequently with ABRAXANE and were mild in the randomized clinical trial. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Asthenia
Asthenia was reported in 47% of patients (8% severe) treated with ABRAXANE in the randomized trial. Asthenia included reports of asthenia, fatigue, weakness, lethargy and malaise.

Other Clinical Events
Rare cases of cardiac ischemia/infarction and thrombosis/embolism possibly related to ABRAXANE treatment have been reported. Alopecia was observed in almost all of the patients. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon. Edema (fluid retention) was infrequent (10% of randomized trial patients); no patients had severe edema.

The following rare adverse events have been reported as part of the continuing surveillance of paclitaxel injection safety and may occur following ABRAXANE treatment: skin abnormalities related to radiation recall as well as reports of maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, conjunctivitis, and increased lacrimation.

Accidental Exposure
No reports of accidental exposure to ABRAXANE have been received. However, upon inhalation of paclitaxel, 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 ABRAXANE overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

DOSAGE AND ADMINISTRATION:
After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for ABRAXANE for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Hepatic Impairment
The appropriate dose of ABRAXANE for patients with bilirubin greater than 1.5 mg/dL is not known.

Dose Reduction
Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe sensory neuropathy during ABRAXANE therapy should have dosage reduced to 220 mg/m^2 for subsequent courses of ABRAXANE. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. For grade 3 sensory neuropathy hold treatment until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of ABRAXANE.

Preparation and Administration Precautions
ABRAXANE is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling ABRAXANE. The use of gloves is recommended. If ABRAXANE (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If ABRAXANE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of ABRAXANE to 30 minutes, as directed, reduces the likelihood of infusion-related reactions (see **PRECAUTIONS: *Injection Site Reaction***).

No premedication to prevent hypersensitivity reactions is required prior to administration of ABRAXANE.

Preparation for Intravenous Administration
ABRAXANE is supplied as a sterile lyophilized powder for reconstitution before use. **AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted sample should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile, polyvinyl chloride (PVC) type IV bag. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Neither freezing nor refrigeration adversely affects the stability of the product. Some settling of the reconstituted suspension may occur. Ensure complete resuspension by mild agitation before use. Discard the reconstituted suspension if precipitates are observed. The suspension for infusion prepared as recommended in an infusion bag is stable at ambient temperature (approximately 25°C) and lighting conditions for up to 8 hours.

HOW SUPPLIED:

Product No.	NDC No.	
103450	68817-134-50	100 mg in a single use vial, individually packaged in a carton.

Storage

Store the vials in original cartons at 20°C to 25°C (68°F to 77°F). Retain in the original package to protect from bright light.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

U.S. Patent Numbers: 5,439,686; 5,498,421; 5,560,933; 5,665,382; 6,096,331; 6,506,405; 6,537,579; 6,749,868; 6,753,006

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ABRAXIS™ ONCOLOGY

A Division of American Pharmaceutical Partners, Inc.
Schaumburg, IL 60173

451031
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ABRAXIS™ ONCOLOGY

451032/Issued: January 2005

Patient Information

Abraxane™ for Injectable Suspension

[generic name=(paclitaxel protein-bound particles for injectable suspension) (albumin-bound)]

WHAT IS ABRAXANE?
ABRAXANE is a prescription cancer medicine. It is injected into a vein and it is used to treat advanced breast cancer.

WHAT IS CANCER?
Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood. A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

HOW DOES ABRAXANE WORK?
ABRAXANE is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. ABRAXANE may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by ABRAXANE causing some of the side effects (see **WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?** below).

WHO SHOULD NOT TAKE ABRAXANE?
ABRAXANE should not be given to patients with dangerously low white blood cell counts.

HOW IS ABRAXANE GIVEN?
ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes.

WHAT PREMEDICATION IS REQUIRED WITH ABRAXANE?
While reactions can occur to any medication, severe allergic reactions to ABRAXANE are uncommon and premedication is not required. However, you should make your doctor aware of any allergies you may have so he/she can determine the course of action required.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF ABRAXANE?

Most patients taking ABRAXANE will experience side effects, although it is not always possible to tell whether such effects are caused by ABRAXANE, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. *Report any unusual symptoms to your doctor.*

Important side effects observed in studies of patients taking ABRAXANE were as follows:

Hair Loss

Complete hair loss, or alopecia, almost always occurs with ABRAXANE. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your ABRAXANE treatment.*

Infections Due to Low White Blood Cell Count

Among the body's defenses against bacterial infections are white blood cells. Between your ABRAXANE treatment cycles, you will often have blood tests to check your white blood cell counts. ABRAXANE usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4°F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

Numbness, Tingling, or Burning in the Hands and/or Feet (Neuropathy)

These symptoms occur often with ABRAXANE and usually get better or go away without medication within three weeks of interrupting treatment. Be sure to tell your doctor about any numbness, tingling or burning that you have in your hands or feet so that he/she can decide the best approach for relief of your symptoms. Sometimes it is necessary to interrupt treatment with ABRAXANE until these symptoms improve. After improvement, treatment can be restarted at a lower dose.

Fatigue and Weakness

ABRAXANE may cause asthenia, fatigue, weakness, lethargy and malaise. These side effects are usually self-limited and do not require dose modification or interruption.

Low Red Blood Cell Count

Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following ABRAXANE treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following ABRAXANE treatment.

Mouth or Lip Sores (Mucositis)

Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the ABRAXANE treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

Joint and Muscle Pain
You may get joint and muscle pain a few days after your ABRAXANE treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Stomach Upset and Diarrhea
Some patients experience nausea, vomiting, and/or diarrhea following ABRAXANE use. If you experience nausea or stomach upset, tell your doctor because medicines can be given that almost always reduce or eliminate these symptoms. Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.*

Heart and Blood Vessel (Cardiovascular) Effects
ABRAXANE may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. You should notify your doctor if you have a history of heart disease.

Irritation at the Injection Site
ABRAXANE may cause irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with ABRAXANE, it is important to talk with your doctor about other possible side effects.

CAN I TAKE ABRAXANE IF I AM PREGNANT OR NURSING A BABY?
ABRAXANE could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with ABRAXANE. *Tell your doctor if you become pregnant or plan to become pregnant while taking ABRAXANE.*

Men should be advised not to father a child while receiving treatment with ABRAXANE.

Because studies have shown the active agent (paclitaxel) in ABRAXANE to be present in the breast milk of animals receiving the active agent, it may be present in human breast milk as well. Therefore, nursing a baby while taking ABRAXANE is NOT recommended. 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 ABRAXANE therapy.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about ABRAXANE. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about ABRAXANE, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration. Based on: ABRAXANE Package Insert 451031/Issued: January 2005

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Schaumburg, IL 60173

451032
Issued: January 2005

Attachment 2: Creation of Reconciled Response Assessment Dataset

To create the Reconciled Response Assessment Dataset, the IRL Response Assessment Dataset was reconciled using a rigorous, conservative, prospective algorithm to minimize bias:

- No reconciliation was performed if:
  - There was agreement between the Investigator and IRL for the best confirmed target lesion response (i.e., CR, PR, SD, or PD).
  - There was a discrepancy resulting simply from errors in calculation of totals which were queries to the Investigator or IRL, as appropriate, and resolved. The corrected data were then used as the response assessment.
- Reconciliation was performed if:

1. A discrepancy occurred for the best confirmed target response assessment because the investigator felt that the patient had progressed (PD) based upon data not available to the IRL (eg, ultrasound, physical exam, other clinical assessments), then the investigator's measurements and assessments would be used.

2. The IRL felt that the case was not interpretable based upon the quality of the films reviewed, or if the target lesions were assessable only by physical exam and/or could not be reviewed radiographically, then the investigator's measurements and assessments would be used.

3. The IRL or the investigator—but not both—felt that the patient had progressed based upon the appearance of a new lesion not noted by the other, then the response assessment is PD.

4. The discrepancy in best confirmed response assessment was due to a discrepancy in the tumor measurements of the same lesion, then the IRL assessment was used.

5. Cases in which a discrepancy arose because the IRL selected different target lesions than those chosen by the investigator, then the IRL assessment was used.

Attachment 3: Taxol Package Insert

TAXOL®
(paclitaxel) INJECTION
(Patient Information Included)

℞ ONLY

WARNING

TAXOL® (paclitaxel) Injection 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%-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.

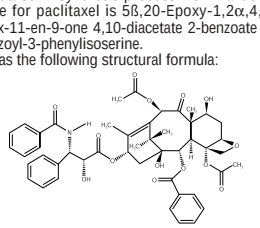
TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of 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.

Paclitaxel is a natural product with antitumor activity. TAXOL is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5ß,20-Epoxy-1,2α,4,7ß,10ß,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-∞) (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-∞) = 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 versus 175 mg/m^2) increased the C_{max} by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC (0-∞) 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 15-135 mg/m^2 given by 1-hour infusions (n=15), 30-275 mg/m^2 given by 6-hour infusions (n=36), and 200-275 mg/m^2 given by 24-hour infusions (n=54) in Phase 1 & 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%-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

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

After intravenous administration of 15-275 mg/m^2 doses of TAXOL (paclitaxel) Injection 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 five 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 two 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 five 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 two 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 six courses. Although the protocol allowed further therapy, only 15% received both drugs for nine 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 six courses.

In both studies, patients treated with TAXOL 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)

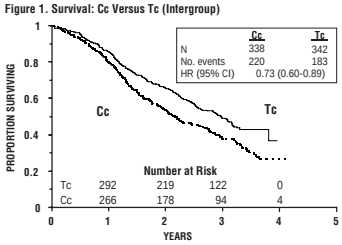
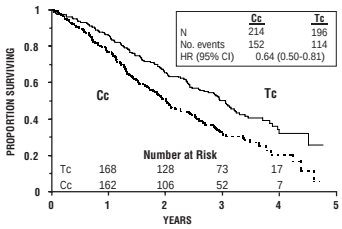


Figure 2. Survival: Cc Versus Tc (GOG-111)



The adverse event profile for patients receiving TAXOL (paclitaxel) Injection 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 five Phase 1 & 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 two studies were 22% (95% CI: 11% to 37%) and 30% (95% CI: 18% to 46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these two 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, administered at two 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% to 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+ - 25.1+ months). Median survival was 11.5 months (range: 0.2-26.3+ 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 two doses (135 or 175 mg/m^2) irrespective of the schedule (3 or 24 hours) and the two 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% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% vs. 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 vs. 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour vs. the 24-hour infusion was 4.0 months vs. 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 & 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 (paclitaxel) Injection or to no further chemotherapy following four 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 three 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 two divided doses on days 1 and 2), or 90 mg/m^2 (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for four courses and either TAXOL 175 mg/m^2 as a 3-hour infusion every 3 weeks for four 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

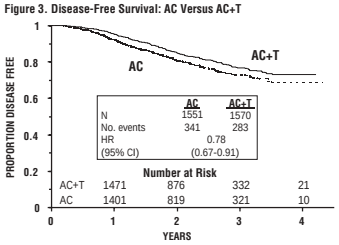
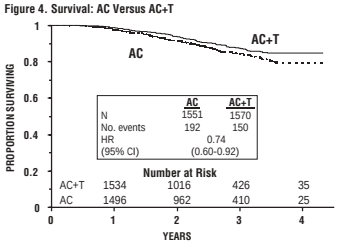


Figure 4. Survival: AC Versus AC+T



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 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

		Disease-Free Survival		Overall Survival	
Patient Subset	**No. of Patients**	**No. of Recurrences**	**Hazard Ratio (95% CI)**	**No. of Deaths**	**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) Injection 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

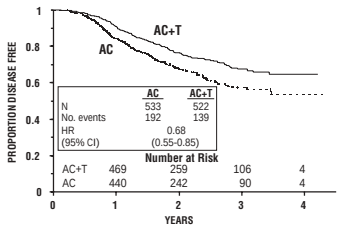


Figure 6. Disease-Free Survival - Receptor Status Positive AC Versus AC+T

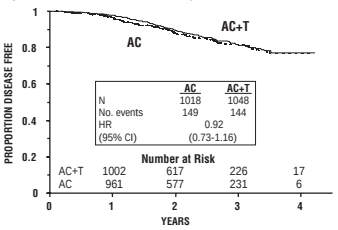


Figure 7. Disease-Free Survival - Premenopausal AC Versus AC+T

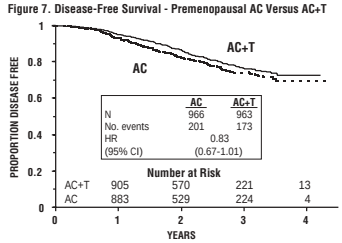
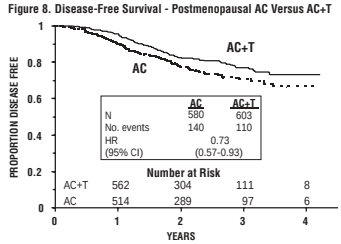


Figure 8. Disease-Free Survival - Postmenopausal AC Versus AC+T



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 three 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 one prior chemotherapeutic regimen. TAXOL was administered in these two 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% to 75%) and 52% (95% CI: 32% to 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 two 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% to 50%).

Phase 3 randomized study- This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive TAXOL 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% to 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 (paclitaxel) Injection 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 one-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	
• One-Year Survival			
- percent of patients	36	40	32

[a] Etoposide (VP) 100 mg/m^2 was administered I.V. 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 seven subscales that measured subjective assessment of treatment. Of the seven, 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 two Phase 2 open label studies support the use of TAXOL 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. 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

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DOXIL® is a registered trademark of ALZA Corporation.

Although the planned dose intensity in the two 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 38-39 mg/m^2/week in both studies, with a similar range (20-24 to 51-61).

Efficacy - The efficacy of TAXOL (paclitaxel) Injection was evaluated by assessing cutaneous tumor response according to the amended ACTG criteria and by seeking evidence of clinical benefit in patients in six 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% to 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 to 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 to 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 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

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® EL (polyoxyethylated castor oil).

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

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%-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.

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^3 (<1000 cells/mm^3 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^3 (>1000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.

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^2 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^2 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 (paclitaxel) Injection 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® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase I trial using escalating doses of TAXOL (110-200 mg/m^2) and cisplatin (50 or 75 mg/m^2) 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. In the absence of formal clinical drug interaction studies, caution should be exercised when administering TAXOL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (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.

Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. 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^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven 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^3.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® 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_2 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**.)

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 rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten 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 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^2 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 (paclitaxel) Injection 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 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^2 to 420 mg/m^2. 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 eight 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 two 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

	Patients [n/total (%)]			
	Neutropenia (Grade IV)		Peripheral Neuropathy (Grades III/IV)	
INDICATION	**Age (yrs)**		**Age (yrs)**	
(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 four courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg/m^2/3 hours every 3 weeks for four 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 eight Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in four 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 two doses (135 or 175 mg/m^2) and two 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.

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Table 10: Summary[a] of Adverse Events in Patients With Solid Tumors Receiving Single-Agent TAXOL (paclitaxel) Injection

		Percent of Patients (n=812)
• Bone Marrow		
- Neutropenia	< 2,000/mm³	90
	< 500/mm³	52
- Leukopenia	< 4,000/mm³	90
	< 1,000/mm³	17
- Thrombocytopenia	< 100,000/mm³	20
	< 50,000/mm³	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 (six courses for the GOG-111 study and up to nine 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/mm³	91[d]	95[d]	96	92
< 500/mm³	33[d]	43[d]	81[d]	58[d]
- Thrombocytopenia				
< 100,000/mm³[e]	21[d]	33[d]	26	30
< 50,000/mm³	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/m²/infusion duration in hours.
[c] Cyclophosphamide (C) or cisplatin (c) dose in mg/m².
[d] p<0.05 by Fisher exact test.
[e] <130,000/mm³ 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 (paclitaxel) Injection 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	< 2,000/mm³	78	98	78	98
	< 500/mm³	27	75	14	67
- Thrombocytopenia	< 100,000/mm³	4	18	8	6
	< 50,000/mm³	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/m²/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/mm³	79	76	48	50
- Thrombocytopenia				
< 50,000/mm³	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/m² cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m², 75 mg/m², or 90 mg/m² (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for four courses.
[d] TAXOL (T) following four courses of AC at a dose of 175 mg/m²/3 hours every 3 weeks for four 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 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 four courses of treatment with TAXOL, two 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	< 2,000/mm³	90	81
	< 500/mm³	28	19
- Thrombocytopenia	< 100,000/mm³	11	7
	< 50,000/mm³	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/m²/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/m².

First-Line NSCLC in Combination: In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either TAXOL (paclitaxel) Injection (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² 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	< 2,000/mm³	89	86	84
	< 500/mm³	74[e]	65	55
- Thrombocytopenia	< normal	48	68	62
	< 50,000/mm³	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/m²/infusion duration in hours; cisplatin (c) dose in mg/m².
[c] TAXOL dose in mg/m²/infusion duration in hours with G-CSF support; cisplatin dose in mg/m².
[d] Etoposide (VP) dose in mg/m² was administered I.V. on days 1, 2 and 3; cisplatin dose in mg/m².
[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 (paclitaxel) Injection 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 two different single-agent TAXOL 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	< 2,000/mm³	100	95
	< 500/mm³	76	35
- Thrombocytopenia	< 100,000/mm³	52	27
	< 50,000/mm³	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/m²/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) Injection at a dose of 135 mg/m² every 3 weeks than in the study utilizing TAXOL at a dose of 100 mg/m² 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 two 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, 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.

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/mm³ in 14% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (<500 cells/mm³) 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/m²/24 hours in combination with cisplatin versus the control arm of cyclosphosphamide 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/m²/24 hours followed by cisplatin) and 65% (TAXOL 250 mg/m²/24 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/m² or 175 mg/m² 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 uncommon, and almost never severe (<50,000 cells/mm³). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ 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 (paclitaxel) Injection 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.

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.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of TAXOL safety.

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 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/m² 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%-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 rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See **PRECAUTIONS: Drug Interactions**.)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of TAXOL safety.

Respiratory: Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of TAXOL safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

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. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34%-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/m² given by 3-hour infusion plus cisplatin 75 mg/m² resulted in a 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 (paclitaxel) Injection 135 mg/m² given by 24-hour infusion plus cisplatin 75 mg/m² 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/m², the incidence of severe neurotoxicity is more common at a TAXOL dose of 175 mg/m² given by 3-hour infusion (21%) than at a dose of 135 mg/m² 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 (paclitaxel) Injection. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving TAXOL 135 mg/m² by 24-hour infusion followed by cisplatin 75 mg/m² 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.

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of TAXOL safety. 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, rare 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.

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 two or three 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.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of TAXOL safety.

Renal: Among the patients treated for Kaposi's sarcoma with TAXOL, five 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 four patients had renal insufficiency with reversible elevations of serum creatinine.

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.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of TAXOL safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were 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 rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten 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.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been received as part of the continuing surveillance of TAXOL safety.

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/m² 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.

Rare reports of conjunctivitis and increased lacrimation have been received as part of the continuing surveillance of TAXOL safety.

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 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 (paclitaxel) Injection 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 (paclitaxel) Injection 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 four courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used four 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 two 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:

1) Reduce the dose of dexamethasone as one of the three premedication drugs to 10 mg PO (instead of 20 mg PO);
2) Initiate or repeat treatment with TAXOL only if the neutrophil count is at least 1000 cells/mm^3;
3) Reduce the dose of subsequent courses of TAXOL by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); and
4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of TAXOL should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. TAXOL should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during TAXOL therapy should have dosage reduced by 20% for subsequent courses of TAXOL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Hepatic Impairment: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: Hepatic**). Recommendations for dosage adjustment for the first course of therapy are shown in Table 17 for both 3- and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

Table 17: Recommendations for Dosing in Patients With Hepatic Impairment Based on Clinical Trial Data[a]

Degree of Hepatic Impairment			
Transaminase Levels		**Bilirubin Levels[b]**	**Recommended TAXOL Dose[c]**
24-hour infusion			
<2 x ULN	and	≤ 1.5 mg/dL	135 mg/m^2
2 - <10 x ULN	and	≤ 1.5 mg/dL	100 mg/m^2
<10 x ULN	and	1.6 - 7.5 mg/dL	50 mg/m^2
≥10 x ULN	or	> 7.5 mg/dL	Not recommended
3-hour infusion			
<10 x ULN	and	≤ 1.25 x ULN	175 mg/m^2
<10 x ULN	and	1.26 - 2.0 x ULN	135 mg/m^2
<10 x ULN	and	2.01 - 5.0 x ULN	90 mg/m^2
≥10 x ULN	or	> 5.0 x ULN	Not recommended

[a] These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for AIDS-related Kaposi's sarcoma).

[b] Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

[c] Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

Preparation and Administration Precautions: TAXOL is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling TAXOL. The use of gloves is recommended. If TAXOL solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If TAXOL contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. (See **PRECAUTIONS: Injection Site Reaction**.)

Preparation for Intravenous Administration: TAXOL must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP, or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. TAXOL solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

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® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of TAXOL since they can cause the stopper to collapse resulting in loss of sterile integrity of the TAXOL solution.

Stability: Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°-25° C (68°-77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours.

HOW SUPPLIED

NDC 0015-3475-30	30 mg/5 mL multidose vial individually packaged in a carton.
NDC 0015-3476-30	100 mg/16.7 mL multidose vial individually packaged in a carton.
NDC 0015-3479-11	300 mg/50 mL multidose vial individually packaged in a carton.

Storage: Store the vials in original cartons between 20°-25°C (68°-77°F). Retain in the original package to protect from light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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PATIENT INFORMATION
TAXOL® INJECTION
(generic name = paclitaxel)

WHAT IS TAXOL?

TAXOL is a prescription cancer medicine. It is injected into a vein and it is used to treat different types of tumors. The tumors include advanced ovary and breast cancer. The tumors also include certain lung cancers (non-small cell) in people who cannot have surgery or radiation therapy. TAXOL may also be used to treat AIDS-related Kaposi's sarcoma.

WHAT IS CANCER?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

HOW DOES TAXOL WORK?

TAXOL is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. TAXOL may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by TAXOL causing some of the side effects. (See **WHAT ARE THE POSSIBLE SIDE EFFECTS OF TAXOL?** below.)

WHO SHOULD NOT TAKE TAXOL?

Patients who have a history of hypersensitivity (allergic reactions) to TAXOL or other drugs containing Cremophor® EL* (polyoxyethylated castor oil), like cyclosporine or teniposide, should not be given TAXOL. In addition, TAXOL should not be given to patients with dangerously low white blood cell counts.

HOW IS TAXOL (PACLITAXEL) INJECTION GIVEN?

TAXOL is injected into a vein [intravenous (I.V.) infusion]. Before you are given TAXOL, you will have to take certain medicines (premedications) to prevent or reduce the chance you will have a serious allergic reaction. Such reactions have occurred in a small number of patients while receiving TAXOL and have been rarely fatal. (See **WHAT ARE THE POSSIBLE SIDE EFFECTS OF TAXOL?** below).

WHAT ARE THE POSSIBLE SIDE EFFECTS OF TAXOL?

Most patients taking TAXOL will experience side effects, although it is not always possible to tell whether such effects are caused by TAXOL, another medicine they may be taking, or the cancer itself. Important side effects are described below; however, some patients may experience other side effects that are less common. *Report any unusual symptoms to your doctor.*

Important side effects observed in studies of patients taking TAXOL were as follows:

– *Allergic reactions.* Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during TAXOL infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash. The likelihood of a serious allergic reaction is lowered by the use of several kinds of medicines that are given to you before the TAXOL (paclitaxel) Injection infusion.

– *Heart and blood vessel (cardiovascular) effects.* TAXOL may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. Your heart function, including blood pressure and pulse, will be monitored while you are receiving the medicine. You should notify your doctor if you have a history of heart disease.

– *Infections due to low white blood cell count.* Among the body's defenses against bacterial infections are white blood cells. Between your TAXOL treatment cycles, you will often have blood tests to check your white blood cell counts. TAXOL usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4° F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

– *Hair loss.* Complete hair loss, or alopecia, almost always occurs with TAXOL. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your TAXOL treatment.*

– *Joint and muscle pain.* You may get joint and muscle pain a few days after your TAXOL treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

– *Irritation at the injection site.* TAXOL sometimes causes irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

– *Low red blood cell count.* Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following TAXOL treatment causing anemia. Some patients may need a blood transfusion to treat the anemia.

Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following TAXOL treatment.

– *Mouth or lip sores (mucositis).* Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the TAXOL treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

– *Numbness, tingling, or burning in the hands and/or feet (neuropathy).* These symptoms occur often with TAXOL and usually get better or go away without medication within several months of completing treatment. However, if you are uncomfortable, tell your doctor so that he/she can decide the best approach for relief of your symptoms.

– *Stomach upset and diarrhea.* Some patients experience nausea, vomiting, and/or diarrhea following TAXOL use. If you experience nausea or stomach upset, tell your doctor. Diarrhea will usually disappear without treatment; however, *if you experience **severe** abdominal or stomach area pain and/or **severe** diarrhea, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects. Because this leaflet does not include all possible side effects that can occur with TAXOL, it is important to talk with your doctor about other possible side effects.

CAN I TAKE TAXOL IF I AM PREGNANT OR NURSING A BABY?

TAXOL could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with TAXOL. *Tell your doctor if you become pregnant or plan to become pregnant while taking TAXOL.*

Because studies have shown TAXOL to be present in the breast milk of animals receiving the drug, it may be present in human breast milk as well. Therefore, nursing a baby while taking TAXOL is NOT recommended.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about TAXOL. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about TAXOL, your doctor and pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

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This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

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