Paclitaxel should be administered under the supervision of a physician experience in the use of cancer chemotherapeutic agents. Appropriate management of plications is possible only when adequate diagnostic and treatment facilities

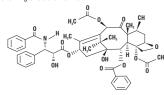
hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated

have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H₂ antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm³ and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm³. 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 paclitaxel.

DESCRIPTION
Paclitaxel Injection is a clear, colorless to slightly yellow viscous solution. It is Pacifiaxel 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. Paclitaxel 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 polyoxyl 35 castor oil, NF, 2 mg of anhydrous citric acid, USP and 49.7% (v/v) dehydrated alcohol, USP. Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via a semi-synthetic process from Taxus baccata. The chemical name for paclitaxel is 58.20.Enoyal. 26.4.6.8.108.13.2.4.psyshydroyatxy.1.1.en.9.psp. 4.10.13.6.psysty.

β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2R, 3S)-N-benzoyl-3-phenylisoserine. aclitaxel has the following structural formula



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{\rm x}H_{\rm y}NO_{\rm x}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217° C. CLINICAL PHARMACOLOGY

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 paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of paclitaxel, 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 paclitaxel at dose levels of 135 and 175 mg/m² 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	Infusion	N	C _{max}	AUC _(0∞)	T-HALF	CL _⊤		
(mg/m ²)	Duration (h)	(patients)	(ng/mL)	(ng•h/mL)	(h)	(L/h/m²)		
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 = Area under the plasma concentration-time curve from time 0 to infinity

tal body clearance ared that with the 24-hour infusion of paclitaxel, a 30% increase in dose (135 It appeared that with the 24-hour influsion of pacifitaxel, a 30% increase in dose (13 mg/m² vs 175 mg/m²) increased the $C_{\rm m}$ by 87%, whereas the AUC_{m²} remained proportional. However, with a 3-hour influsion, for a 30% increase in dose, the $C_{\rm max}$ and AUC_{m²} were increased by 68% and 89%, respectively. The mean apparen volume of distribution at steady state, with the 24-hour influsion of paclitaxel, ranger from 227 to 688 L/m², indicating extensive extravascular distribution and/or tissue hinding of nacilitaxel

binding of pacitiaxer. The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m² given by 1-hour infusions (n=15), 30 to 275 mg/m² given by 6-hour infusions (n=36), and 200 to 275 mg/m² given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CL₁ and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of paclitaxel 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 mcg/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not

the presence of cimetidine, rantitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. After intravenous administration of 15 to 275 mg/m² doses of paclitaxel as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m² dose of radiolabeled paclitaxel as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α -hydroxypaclitaxel, accounted for the balance. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-p-hydroxypaclitaxel, aby 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. f paclitaxel may also be altered *in vivo* as a result of interactions with compounds hat are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See PRECAUTIONS: Drug Interactions.)

PHECAUTIONS: 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 pilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin <2 The adverse event profile for patients receiving paclitaxel in combination with

First-Line Data: The safety and efficacy of paclitaxel followed by cisplatin in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in 2, Phase 3 multicenter, randomized, controlled trials. In an Intergroup study led by the European Organization for Research and Treatment of Cancer involving the Scandinavian Group NOCOVA, the National Cancer Institute of Canada, and the he European Organization for Research and Treatment of Canada, and the Scottish Group, NOCOVA, the National Cancer Institute of Canada, and the Scottish Group, 680 patients with Stage III., or IV disease (optimally or non optimally debulked) received either paclitaxel 175 mg/m² (flor) or cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m² (Cc) for a median of 6 courses. Although the protocol allowed further therapy, only 15% received either paclitaxel and the stage III. or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) received either paclitaxel 135 mg/m² infused over 24 hours followed by cisplatin 75 mg/m² followed by cisplatin 75 mg/m² for 6

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

TABLE 2A: EFFICACY IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY (n=96) (n=106) (n=99) (n=106)

Response

TABLE 2A: FEFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA

	(no	Int n-optimally	ergroup / debulke	d subset)		G-111
		C750a				
	c75		c75	c75		c75
	(n=218)		(n=227)	(n-196)		(n=214
• Clinical Response	(n=153)		(n=153)	(n=153)		(n=12
-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 (HR)c		0.73			0.64	
-95% CI ^c		0.58-0.91			0.50-0.81	

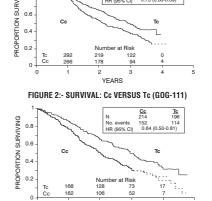
cisplatin doses in mg/m2 Among patients with measurable disease only.
Uncertified for the Intergroup Study, Stratified for Study GOG-111.

TABLE 2B: EFFICACY IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA INTERGROUP STUDY

T175/3 ^a		C750a
c75		c75
(n=342)		(n=338)
(n=162)		(n=161)
59		45
	0.014	
15.3		11.5
	0.0005	
	0.74	
	0.63-0.88	
35.6		25.9
	0.0016	
	0.73	
	0.60-0.89	
	c75 (n=342) (n=162) 59	C75 (n=342) (n=162) 59 0.014 15.3 0.0005 0.74 0.63-0.88 35.6 0.0016 0.73

Paclitaxel dose in mg/m²/infusion duration in hours; cyclophosicisplatin doses in mg/m².
Among patients with measurable disease only.

FIGURE 1:- SURVIVAL: Cc VERSUS Tc (INTERGROUP)



2 YEARS

no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m²), 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 Patz: The safety and efficacy of paclitaxel followed by cisplatin in natients (>90%) administered over 24 hours by continuous infusion. Response rates in these 2 studies were 22% (95% CI, 11-37%) and 30% (95% CI, 18-46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these 2 studies measured from the first day of treatment was 7.2 months (range, 3.5-15.8 months) and 7.5 months (range, 6.3-17.4 months), respectively. The median survival was 8.1 months (range, 0.2-36.7 months) and 15.9 months (range, 0.2-36.7 months) and 15.9 months

TABLE 3: EFFICACY IN THE PH	HASE 3 SECO	ND-LINE OVA	RIAN CARCII	NOMA STUDY	
	175/3	175/24	135/3	135/24	• No. (
	(n=96)	(n=106)	(n=99)	(n=106)	1-3
• Response					-
-rate (percent)	14.6	21.7	15.2	13.2	4-9
-95% Confidence Interval	(8.5-23.6)	(14.5-31.0)	(9.0-24.1)	(7.7-21.5)	10+
Time to Progression					104
-median (months)	4.4	4.2	3.4	2.8	• Tum
-95% Confidence Interval	(3.0-5.6)	(3.5-5.1)	(2.8-4.2)	(1.9-4.0)	≤2
Survival					
-median (months)	11.5	11.8	13.1	10.7	>2 and
-95% Confidence Interval	(8.4-14.4)	(8.9-14.6)	(9.1-14.6)	(8.1-13.6)	
Analyses were performed as pl					
protocol, by comparing the 2 d					
(3 or 24 hours) and the 2 sche					
mg/m ² dose had a response ra	ate similar to	that for those	e receiving t	ne 135 ma/m²	

mg/m² dose nad a response rate similar to that for those receiving the 135 mg/m² dose: 18% versus 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% versus 17% (p=0.50). Patients receiving the 175 mg/m² dose of paclitaxel had a longer time to progression than those receiving the 135 mg/m² dose: median 4.2 versus 3.1 months (p=0.03). The those receiving the 135 mg/m² dose: median 4.2 versus 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour versus the 24-hour infusion was 4.0 months versus 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 135 mg/m² dose (p=0.92). Median survival was 11.7 months for patients receiving the 3-hour infusion of paclitaxel and 11.2 months for patients receiving the 3-hour infusion of paclitaxel 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.

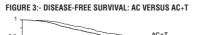
Paclitaxel remained active in patients who had developed resistance to platinum-containing therapy (Jeffierd as tumor progression while on or tumor relans within

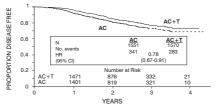
racitaxeir remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, a platinum-containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 and 2 clinical studies. The adverse event profile in this Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 second-line ovarian carcinoma study are described in the ADVERSE REACTIONS section in tabular (TABLES 10 and 12) and narrative form.

12) and narrative form. The results of this randomized study support the use of paclitaxel at doses of 135 to 175 mg/m², 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

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 paclitaxel or to no further chemotherapy following 4 courses of doxorubicin and cyclophosphamide (AC). This multicenter trial was conducted in women with histologically positive lymph nodes following either a mastectomy or segmental mastectomy and nodal dissections. The 3 x 2 factorial study was designed to assess the efficacy and safety of 3 different dose levels of doxorubicin (A) and to evaluate the effect of the addition of pacilitaxel administeract following the completion of AC therapy. After stratification for the 3 x 2 factorial study was designed to assess the efficacy and safety of 3 different dose levels of doxorubicin (A) and to evaluate the effect of the addition of paclitaxel 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/m² and doxorubicin at doses of either 60 mg/m² (no day 1), 75 mg/m² (in 2 divided doses on days 1 and 2), or 90 mg/m² (in 2 divided doses on days 1 and 2) with prophylactic G- CSF support and ciprofloxacin) every 3 weeks for 4 courses and either paclitaxel 175 mg/m² as a 3-hour infusion every 3 weeks for 4 additional courses or no additional chemotherapy. Patients whose tumors were positive were to receive subsequent tamoxifen treatment (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities. At the time of the current analysis, median follow-up was 30.1 months. Of the 2066 patients who were hormone receptor positive, 93% received tamoxifen. The primary analyses of disease-free surrival and overall survival used multivariate Cox models, which included paclitaxel 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 paclitaxel 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/m² had no effect on either disease-free survival or overall survival.





ibed in the **ADVERSE REACTIONS** section in tabular (**TABLES 10** and

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

Phase 2 open-label studies: Two studies were conducted in 53 patients previously reated with a maximum of 1 prior chemotherapeutic regimen. Paclitaxel was administered in these 2 trials as a 24-hour infusion at initial doses of 250 mg, Subset alralyses. Subsets deelined by Variables to known prognosist importation 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 pacifitaxel for both disease-free and overall survival in all of the larger subsets with nee exception; patients with receptor-positive tumors had a smaller reduction in hazard (HR=0.92) for disease-free survival with paclitaxel than other groups. Results of subset analyses are shown in TABLE 4.

treated with a maximum of 1 prior chemotherapeutic regimen. Paclitaxel was administered in these 2 trials as a 24-hour infusion at initial doses of 250 mg/m² (with G-CSF support) or 200 mg/m². The response rates were 57% (95% Cl, 37-75%) and 52% (95% Cl, 32-72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of paclitaxel was 200 mg/m² as a 24-hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, for a response rate of 30% (95% Cl, 15-50%).

**Phase 3 randomized study: This multicenter trial was conducted in patients previously treated with 1 or 2 regimens of chemotherapy. Patients were randomized to receive paclitaxel at a dose of either 175 mg/m² or 135 mg/m² 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% Cl, 22-30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 81 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).

ven in the following table TABLE 5: EFFICACY CHEMOTHERAPY OR V	' IN BREAST CANCE		
	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	
e adverse event profile d			

Phase 3 study was consistent with that seen for the pooled analysis of data from 112 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.

Positive for either estrogen or progesterone receptors.

Negative or missing for both estrogen and progesterone receptors (both missing: n=15).

Negative or missing for both estrogen and progesterone receptors (both missing: n=15).

Non-Small (Cell Lung Carcinoma (NSCLC)

In a Phase 3 open-label randomized study conducted by the ECOG, 599 patients were randomized to either paclitaxel (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², paclitaxel (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², paclitaxel (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², paclitaxel (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).

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

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

a Etoposide (VP) 100 mg/m² was administered IV on days 1, 2, and 3.

Compared to cisplatin/etoposide.

In the ECOG study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had 7 subscales that measured subjective assessment of treatment. Of the 7, the Lung Cancer Specific Symptoms subscale favored the paclitaxel 135 mg/m²/24 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 paclitaxel 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 paclitaxel 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.

and narrative form.

AIDS-Related Kaposi's Sarcoma
Data from 2, Phase 2 open-label studies support the use of paclitaxel as secondline therapy in patients with AIDS-related Kaposi's sarcoma. Fifty-nine of the 85
patients enrolled in these studies had previously received systemic therapy, including
interferon alpha (32%), DaunoXome® (31%), DOXIL® (2%), and doxorubicin
containing chemotherapy (42%), with 64% having received prior anthracyclines.
DaunoXome® is a registered trademark of Gilead Sciences, Inc.
DOXIL® is a registered trademark of ALZA Corporation.

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

tolerate, prior systemic therapy. In Study CA139-174, patients received paclitaxel at 135 mg/m² as a 3-hour infusion should be performed during subsequent therapy with paclitaxel injection.

Pregnancy

Paclitaxel patients received paclitaxel at 100 mg/m² as a 3-hour infusion every of the daily maximum recommended hum observed, patients were to receive 155 mg/m² and 175 mg/m² in subsequent courses. Hematopoietic growth factors were not to be used initially. In Study 26139-281, patients received paclitaxel at 100 mg/m² as a 3-hour infusion every 2 weeks (intended dose intensity 50 mg/m²/week). In this study patients could be performed during subsequent therapy with paclitaxel injection.

Pregnancy

Paclitaxel lnjection can cause fetal harm when administered to a pregnant woman. And fetotoxicity. (See WARNINGS.)

3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/ m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, Pregnancy Category D. (See WARNINGS.)

support was to be initiated as indicated; the dose of paclitaxel was not increased. The dose intensity of paclitaxel 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 (T₁), 88% had a CD4 count <200 cells/mm3 (I₁), and 97% had poor risk considering their systemic illness (S₁)

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

TABLE 7: EXTENT OF DISEASE AT STUDY ENTRY

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

Although the planned dose intensity in the 2 studies was slightly different (45 mg/m²/week in Study CA139-174 and 50 mg/m²/week in Study CA139-281), delivered dose intensity was 38 to 39 mg/m²/week in both studies, with a similar range (20-24

Efficacy: The efficacy of paclitaxel was evaluated by assessing cutaneous tumo response according to the amended ACTG criteria and by seeking evidence of clinical benefit in patients in 6 domains of symptoms and/or conditions that are commonly related to AIDS related Kaposi's sarcoma.

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

iously raised lesions.

TABLE 8: OVERALL BEST RESPONSE (AMENDED ACTG CRITERIA)

	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% Cl, 7.0-11.0 months) for the patients who had previously received systemic therapy. The median time to progression was 6.2 months (95% Cl, 4.6-8.7 months).

**Additional Clinical Benefit: Most data on patient benefit were assessed retrospectively (plans for such analyses were not included in the study protocols). Nonetheless, clinical descriptions and photographs indicated plans have the study protocols. Nonetheless, clinical descriptions and photographs indicated plans have the study protocols. Initial descriptions and photographs indicated clear benefit in some patients, ncluding instances of improved pulmonary function in patients with pulmonary nvolvement, improved ambulation, resolution of uclers, and decreased analgesic equirements in patients with Kaposi's sarcoma (KS) involving the feet and resolution

f facial lesions and edema in patients with KS involving the face, extremities, and 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 are 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 pacilitaxel 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 the patients of the patients of the patients of the patients.

combination with cisplatin.

Paclitaxel Injection 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 Carcinama)

combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless

clinically contraindicated.

Paclitaxel Injection, 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.

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

CONTRAINDICATIONS

Paclitaxel Injection is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in polyoxyl 35 castor oil, NF.

Paclitaxel Injection is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in polyoxyl 35 castor oil, NF.

Paclitaxel Injection ontains 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 paclitaxel may be exacerbated in patients with solid be exercised when administering paclitaxel injection to such such patients with dose reduction as recommended in DOSAGE AND ADMINISTRATION, TABLE 17.

TABLE 17.

Table 17.

Kaposi's sarcoma.

CONTRAINDICATIONS

Paclitaxel Injection is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in polyoxyl 35 castor oil, NF.

Paclitaxel Injection should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/mm³ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm³.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H, antagonists. (See DOSAGE AND ADMINISTRATION.) Patients who experience severe hypersensitivity reactions to paclitaxel injection 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. Paclitaxel Injection should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³ (<1000 cells/mm³ for patients with KS). Frequent monitoring of blood counts should be instituted during paclitaxel injection treatment. Patients should not be re-treated with subsequent cycles of paclitaxel injection until neutrophils recover to a level >100,000 cells/mm³ (>1000 cells/mm³ for patients with KS) and platelets recover to a level >100,000 cells/mm³ (>1000 cells/mm³ for patients during paclitaxel injection therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paccitaxel injection mitoring should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel injection.

should be performed during subsequent therapy with paclitaxel injection.

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/m² 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 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 notiving infants, it is recommended that nursing be discontinued when receiving paclitaxel injection in pediatric patients have not been contact the undiluted concentrate with plasticized notiving infants, it is recommended that nursing be discontinued when receiving paclitaxel injection in pediatric patients have not been contact the undiluted concentrate with plasticized notiving infants, it is recommended that nursing be discontinued when receiving paclitaxel injection in pediatric patients have not been contact the undiluted concentrate with plasticized notiving infants, it is recommended that nursing be discontinued when receiving paclitaxel injection in pediatric patients have not been contact the undiluted concentration in pregnant.

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- ethyllexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel with death) in a clinical trial in pediatric patients have intrused established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients have intrused.

demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin. The metabolism of paclitaxel injection is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel injection is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, traconazole, ketoconazole, netazodone, nelfinavir, ritonavir, saquinavir, and tellithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. (See CLINICAL PHARMACOLOGY.)
Caution should also be exercised when paclitaxel injection is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. (See CLINICAL PHARMACOLOGY.)
Potential interactions between paclitaxel injection. a substrate of CYP3A4 and

PHARMACOLOGY.)
Potential interactions between paclitaxel injection, 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

Paclitaxel injection therapy should not be administered to patients with baseline neutrophil counts of less than 1500 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 paclitaxel injection. Patients should not be retreated with subsequent cycles of paclitaxel injection until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for 7 days or more) during a course of paclitaxel injection 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, paclitaxel injection, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm³.

Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing polyoxyl 35 castor oil (eg. cyclosporin for injection concentrate and teniposide for injection should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H, 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 trequiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel injection and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel injection.

Cardiovascular

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally apalitaxel injection interruptions because of initial paclitaxel injection interruptions because of initial paclitaxel injection interrupt

paclitaxel injection infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel injection infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See WARNINGS.) When paclitaxel injection is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. (See ADVERSE REACTIONS.)

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 paclitaxel injection at a different site, ie, "recall," has been reported.

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of paclitaxel has not been studied.
Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m² basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo and fetotoxicity. (See WARNINGS.)

Pregnancy

Pediatric Use The safety and effectiveness of paclitaxel injection in pediatric patients have not beer

injection solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined The toxicity is most likely attributable to the high dose of the ethanol component administration sets.

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

Drug Interactions

In a Phase 1 trial using escalating doses of paclitaxel (110-200 mg/m²) and cisplatin (50 or 75 mg/m²) given as sequential infusions. myelosunpression was

resulted in significant leaching of DEHP.

Drug Interactions
In a Phase 1 trial using escalating doses of paclitaxel (110-200 mg/m²) and cisplatin (50 or 75 mg/m²) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (ie., paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel injection is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel injection is concomitantly administered with known substrates (eg., midazolam), inhibitors (eg., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg., rifampin and carhamazenine) of CYP3A4. (See CLINICAL PHARMACOLOGY.)

for use in this population.

Geriatric Use

Of use in this population.

NSCLC, and 1570 patients who were randomized to receive paclitaxel in the deflectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the deflectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or MSCLC, and 1570 patients who were randomized to receive paclitaxel in the deflectiveness in younger group. **TABLE 9** presents the incidences neuropathy in clinical studies according to age. nces of Grade IV neutropenia and seve

TABLE 9: SELECTED ADVERSE EVENTS IN GERIATRIC PATIENTS RECEIVING PACLITAXEL IN CLINICAL STUDIES

Patients (n/total [%])

		Patients (n/total [%])		
	Neuti	ropenia	Peripheral Neuropathy	
	(Grade IV)		(Grades III/IV)	
CATION	Ag	Age (y)		(y)
udy/Regimen)	≥65	<65	≥65	<65
RIAN Cancer				
ergroup First-Line/ '5/3 c75ª)	34/83 (41)	78/252 (31)	24/84 (29)*b	46/255 (18) ^b
)G-111 First-Line/ 35/24 c75ª)	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
ase 3 Second-Line/ 75/3°)	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
ase 3 Second-Line/ 75/24°)	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
ase 3 Second-Line/ 35/3°)	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
ase 3 Second-Line/ 35/24°)	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
ase 3 Second-Line bled)	47/82 (57)*	141/319 (44)	1/83 (1)	2/320 (1)
ıvant BREAST Cancer		•		
ergroup/AC followed T ^d)	56/102 (55)	734/1468 (50)	5/102 (5) ^e	46/1468 (3)
AST Cancer After Fail	ure of Initial	Therapy		
ase 3/T175/3°)	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
ase 3/T135/3°)	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
-Small Cell LUNG Car	ncer			
G/T135/24 c75 ^a)	58/71 (82)	86/124 (69)	9/71 (13)1	16/124 (13)
e 3/T175/3 c80 ^a)	37/89 (42)*	56/267 (21)	11/91 (12)*	11/271 (4)
.05				
litaval daca in ma/m²/i	nfucion durat	ion in hours: o	ionlatin dococ	in ma/m²

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

Intergroup First-Line Ovarian Cancer study (see TABLE 11).

Paclitaxel dose in mg/m³/infusion duration in hours.

Paclitaxel (T) following 4 courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg m²/3hours every 3 weeks for 4 courses.

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

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 paclitaxel. Two hundred and seventy-five patients were treated in 8, Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m² administered over 24 hours (in 4 of these studies, 6-CSF was administered over 24 hours (in 4 of these studies, 6-CSF was administered over 175 mg/m²) and 2 schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six mg/m²) and 2 schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six mg/m²) administered over 175 mg/m²) administered over 175 mg/m²) administered over 175 mg/m²) administered

nts with breast carcinoma received paclitaxel (135 or 175 mg/m²) administered

over 3 hours in a controlled study. TABLE 10: SUMMARY^a OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS

		Percent of Patients (n=812)
Bone Marrow		
-Neutropenia	<2000/mm ³	90
	<500/mm³	52
-Leukopenia	<4000/mm ³	90
	<1000/mm³	17
-Thrombocytopenia	<100,000/mm³	20
	<50,000/mm ³	7
-Anemia	<11 g/dL	78
	<8 g/dL	16
-Infection		30
-Bleeding		14
-Red Cell Transfusions	1	25
-Platelet Transfusions		2
 Hypersensitivity Reac 	tion ^b	
-All		41

FIGURE 4:- SURVIVAL: AC VERSUS AC+T

ubset analyses. Subsets defined by variables of known progni

221

274

129

374

331

0.4 - No. events 533 AC+T 522 HR 192 0.68 139 (0.55-0.85) Number 1

293 0.92

1310

1096

1929

1055

0.6

nor Size (cm)

Positive^a 2066

Unknown^b

Positive for either estron

TABLE 4: SUBSET ANALYSES-ADJUVANT BREAST CARCINOMA STUDY

0.93 (0.66-1.31)

(0.51-1.08)

0.83

0.68 (0.55-0.85) gesterone receptor

FIGURE 5:- DISEASE-FREE SURVIVAL-RECEPTOR STATUS NEGATIVE/UNKNOWN

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

2 YEARS

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

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

AC AC+T 580 603 140 0.73 110 (0.57-0.93)

Number at Risk 204 111

N AC No. events 1018 HR 149 0.92 (95% Cl) (0.73-1.16)

(0.54-0.93)

153 0.79 (0.57-1.08)

AC+T 1570 150

Disease-Free Surivival No. of Hazard Ratio Recurrences (95% CI) Overall Surivival No. of Hazard Ratio Deaths (95% CI)

What is the amoniture and what is the amoniture and about Pacitizate Injection can about pure about the carbon pure about a pacitizate Injections can about a pacitizate Injection selectizate Injection can apply who reads to death and must be readed in a pacitizate Injection.

Serious allergic reactions in people who receive Pacitizate Injection.

Serious allergic tractions in people who receive Pacitizate Injection and non-prescription and anon-prescription and anon-prescription and anon-prescription and anon-prescription and anon-prescription and non-prescription is in peregnant or plant to become pregnant.

Feelings to a list of them and subjection is sufficient in peregnant or plan to become pregnant or plan to reash-feeding or plan to beast-feeding or plan to become pregnant or plan to the antiplection is a prescription medicine.

Injection is safe or effective in childrant injection if the antiplection is a prescription medicine or trash your hard the provider and pharmacis when you get a new medicines on the propagate injection or become pregnant or plan to become pregnant or become preg

-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
Based on worst course analysis.	

Based on worst course analysis.

All patients received premedication.

During the first 3 hours of infusion.

Severe events are defined as at least Grade III toxicity.

None of the observed toxicities were clearly influenced by age.

Disease-Specific Adverse Event Experiences

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

TABLE 11: FREQUENCY^a OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-LINE

		Percent of Patients				
		Intergrou	Intergroup GO			
		T175/3b	C750 ^c	T135/24b	C750°	
		c75°	c75 ^c	c75 ^c	c75 ^c	
		(n=339)	(n=336)	(n=196)	(n=213)	
• Bone Marrow						
-Neutropenia	<2000/mm ³	91 ^d	95 ^d	96	92	
	<500/mm ³	33 ^d	43 ^d	81 ^d	58 ^d	
-Thrombocytopenia	<100,000/mm ^{3e}	21 ^d	33 ^d	26	30	
	<50,000/mm ³	3 ^d	7 ^d	10	9	
-Anemia	<11 g/dL ^f	96	97	88	86	
	<8 g/dL	3 ^d	8 ^d	13	9	
-Infection		25	27	21	15	
-Febrile Neutropenia		4	7	15 ^d	4 ^d	
• Hypersensitivity React	ion					
-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	

-Any symptoms

. ueinn duration in houre

In the GOG-111 study neurotoxicity was collected as peripheral neuropathy and in the oxicity was collected as either neuromotor or

Severe events are defined as at least Grade III toxicity. NC Not Collected

Second-Line Ovary
For the 403 patients who received single-agent paclitaxel in the Phase 3 second-line ovarian arcinoma 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

OVAITIAN CARONONIA STODT					
	Percent of Patients				
		175/3 ^b	175/24b	135/3 ^b	135/24 ^b
		(n=95)	(n=105)	(n=98)	(n=105)
• Bone Marrow					
-Neutropenia	<2000/mm ³	78	98	78	98
	<500/mm³	27	75	14	67

-Thrombocytopenia	<100,000/mm ³	4	18	8	6
	<50,000/mm ³	1	7	2	1
-Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
-Infection		26	29	20	18
• Hypersensitivity React	ion ^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	-Any symptoms		35	21	25
-Severe symptoms†		0	3	0	2

-Severe symptoms*

Based on worst course analysis.

Paclitaxel dose in mg/m²/infusion duration in hours.

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

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 sively than other patients.

TABLE 49. EDECLIENCY2 OF IMPORTANT CEVERED ADVERGE EVENTS IN THE DILACE O

ADJUVANT BREAST CARCINOMA STUDY					
		Percent of Patients			
		Early Population		Total Population	
		AC ^c (n=166)	AC ^c followed by T ^d (n=159)	AC ^c (n=1551)	AC ^c followed by T ^d (n=1570)
• Bone Marrow ^e					
-Neutropenia	<500/mm ³	79	76	48	50
-Thrombocytopenia	<50,000/mm ³	27	25	11	11
-Anemia	<8 g/dL	17	21	8	8
-Infections		6	14	5	6
-Fever Without Infe	ction	-	3	<1	1
Hypersensitivity Reaction ^t		1	4	1	2
Cardiovascular Events		1	2	1	2
Neuromotor Toxicity		1	1	<1	1
 Neurosensory Toxio 	city	-	3	<1	3
 Myalgia/Arthralgia 		-	2	<1	2
Nausea/Vomiting		13	18	8	9
Mucositis		13	4	6	5
Bacad on worst co	urea analyeie				

Severe events are defined as at least Grade III toxicity.

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

Paclitaxel (T) following 4 courses of AC at a dose of 175 mg/m²/3 hours every 3 weeks for 4

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

The incidence of febrile neutropenia was not reported in this study.
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 paclitaxel following AC therapy may be compared with AC therapy alone. Compared to patients who received AC alone, patients who received AC followed by paclitaxel experienced more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV heurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional 4 courses of treatment with paclitaxel, 2 deaths (0.1%) were attributed to treatment. During paclitaxel treatment, grade IV/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

increased with higher doses of doxordocina.

Fereast Cancer After Failure of Initial Chemotherapy

For the 458 patients who received single-agent paclitaxel in the Phase 3 breast carcinoma study,
the following table shows the incidence of important adverse events by treatment arm (each arm
uses administrated by a 2 bear infraision.

able shows the influence of importance of the property of the

	ADJUVANT CHEN	MOTHERAPY	
		Percent o	f Patients
		175/3 ^b (n=229)	135/3 ^b (n=229)
Bone Marrow			
-Neutropenia	<2000/mm ³	90	81
	<500/mm ³	28	19
-Thrombocytopenia	<100,000/mm ³	11	7
	<50,000/mm ³	3	2
-Anemia	<11 g/dL	55	47
	<8 g/dL	4	2
-Infection		23	15
-Febrile Neutropenia		2	2
Hypersensitivity React	ion ^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
Based on worst course	analysis		

All patients received premedication. Severe events are defined as at least Grade III toxicity.

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Anat is written for healthcare rovider. You can ask your harmacist or healthcare aditaxel laid and grown in an orderly, ontrolled way. Cell division and growh are necessary or the human body to erform its functions and to repair itself, when seessary. Cancer cells and grown in an orderly to recessary. Cancer cells and growing fast mot rowth. The reasons for this because they are not yet ally understood.

tumor is a mass of healthy cells that are viding and growing healthy ody, tissue, it is known so a malignant tumor. A nalignant tumor can spread metastasize) from its righe body if not found and eated early.

First-Line NSCLC in Combination ted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either paclitaxel (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², paclitaxel (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		
		T135/24b	T250/24°	VP100 ^d
		c75	c75	c75
		(n=195)	(n=197)	(n=196)
Bone Marrow				
-Neutropenia	<2000/mm ³	89	86	84
	<500/mm ³	74e	65	55
-Thrombocytopenia	<normal< td=""><td>48</td><td>68</td><td>62</td></normal<>	48	68	62
	<50,000/mm ³	6	12	16
-Anemia	< normal	94	96	95
	<8 g/dL	22	19	28
-Infection		38	31	35
 Hypersensitivity React 	ion ^r			
-All		16	27	13
-Severe†		1	4e	1
• Arthralgia/Myalgia				
-Any symptoms		21e	42°	9
-Severe symptoms†		3	11	1
Nausea and 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€	8
 Cardiovascular Events 				
-Any symptoms		33	39	24
-Severe symptoms†		13	12	8

Based on worst course analysis.
 Paclitaxel (T) dose in mg/m²/infusion duration in hours; cisplatin (c) dose in mg/m².
 Paclitaxel dose in mg/m²/infusion duration in hours with G-CSF support; cisplatin dose in mg/

oposide (VP) dose in mg/m² was administered IV on days 1, 2, and 3; cisplatin dose in mg/

All patients received premedication.

Severe events are defined as at least Grade III toxicity.

Toxicity was generally more severe in the high-dose paclitaxel treatment arm (T250/c75) than in the low-dose paclitaxel arm (T135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose paclitaxel arm experienced more arthraligia/myalgia of any grade and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

Kaposi's Sarcoma

The following table shows the frequency of important adverse events in the 85 patients with KS treated with 2 different single-agent paclitaxel regimens.

TABLE 16: FREQUENCY^a OF IMPORTANT ADVERSE EVENTS IN THE AIDS-RELATED KAPOSI'S

	UA	RUUNA STUDIES		
		Percent of Patients		
		Study CA 139-174 Paclitaxel 135/3b q 3 wk	Study CA 139-281 Paclitaxel 100/3b q 2 wk	
		(n=29)	(n=56)	
• Bone Marrow				
-Neutropenia	<2000/mm ³	100	95	
	<500/mm ³	76	35	
-Thrombocytopenia	<100,000/mm ³	52	27	
	<50,000/mm ³	17	5	
-Anemia	<11 g/dL	86	73	
	<8 g/dL	34	25	
-Febrile Neutropenia		55	9	
• Opportunistic Infec	tion			
-Any		76	54	
-Cytomegalovirus		45	27	
-Herpes Simplex		38	11	
-Pneumocystis carii	nii	14	21	
-M. avium intracellu	lare	24	4	
-Candidiasis, esopha	ageal	7	9	
-Cryptosporidiosis		7	7	
-Cryptococcal menir	ngitis	3	2	
-Leukoencephalopat	hy	_	2	
• Hypersensitivity Re	eaction ^e			
-All		14	9	
• Cardiovascular				
-Hypotension		17	9	
-Bradycardia		3	_	
• Peripheral Neuropa	athy			
-Any		79	46	
-Severe†		10	2	
• Myalgia/Arthralgia				
-Any		93	48	
-Severe		14	16	
• Gastrointestinal				
-Nausea and Vomiti	ng	69	70	
-Diarrhea		90	73	

• Discontinuation for drug toxicity

| Based on worst course analysis.
| Paclitaxel dose in mg/m²/infusion duration in hours.
| All patients received premedication.

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 paclitaxel at a dose of 135 mg/m² every 3 weeks than in the study utilizing paclitaxel 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 2 studies with respect to dose escalation and use of etic 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

nitant treatment with protease inhibitors, whose effect on paclitaxe

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 paclitaxel in clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received paclitaxel in combination with cisplatin or in patients with breast cancer who received paclitaxel 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 paclitaxel for the treatment of ovarian, breast, or lung carcinoma or Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections (including opportunistic infections, see TABLE 16), and febrile neutropenia. These patients require a lower dose intensity and supportive care, (see CLINICAL STUDIES: AIDS-related Kaposi's Sarcoma.) Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described. Elevated liver function tests and renal toxicity have a higher incidence in KS patients as compared to patients with solid tumors. in KS patients as compared to patients with solid tumors

Hematologic Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. 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-hou 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

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 paclitaxel 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 cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the paclitaxel plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the paclitaxel plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the paclitaxel (sisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When paclitaxel followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (paclitaxel 135 mg/m²/24 hours followed by cisplatin) and 65% (paclitaxel 250 mg/m²/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

etoposide. Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all

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/m³ 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 reported. 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 nadii. 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 paclitaxel 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%

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)
In clinical trials, all patients received premedication prior to paclitaxel administration (see WARNINGS and PRECAUTIONS: Hypersensitivity Reactions). The frequency and severify of HSRs were not affected by the dose or schedule of paclitaxel 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 paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain, and tachycardia. Abdominal pain, pain in the extremities, diaphoresis, and hypertension were also noted.

noted.

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

Chills and shock, and reports of back pain in association with hypersensitivity reactions have

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

anthracyclinic inertapy. Significant cardiovascular events possibly related to single-agent pacintaxe 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 paclitaxel 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 paclitaxel in combination with cisplatin in the Phase 3 study, significant cardiovascular events occurred in 12 to 13%. This apparent ular events possibly related to single-agent paclitaxel occurred in

se in cardiovascular events is possibly due to an increase in cardiovascular risk factors in

ogram (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 lities, sinus bradycardia, sinus tachycardia, and premature beats. Among patients with ormal ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of

EGG abnormalities.

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

Atrial fibrillation and supraventricular tachycardia have been reported.

Interstitial pneumonia, lung fibrosis, and pulmonary embolism have been reported. Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy. Pleural effusion and respiratory failure have been reported.

Pleural etrusion and respiratory failure have been reported.

Neurologic

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

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Paresthesia commonly occurs in the form of hyperesthesia. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34 to 51% from course 2 to 10. Peripheral neuropathy was the cause of naclitaxel discontinuation in 1% of all natients. Sensory symptoms have after the first course of treatment and in 34 to 51% from course 2 to 10. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. In the Intergroup first-line ovarian carcinoma study (see **TABLE 11**), neurotoxicity included reports of neuromotor and neurosensory events. The regimen with paclitaxel 175 mg/m² given by 3-hour infusion plus cisplatin 75 mg/m² resulted in greater incidence and severity of reports of neuromotor and neurosensory events. The regimen with pacitaxel 1/3 mg/m² given by 3-hour infusion plus cisplatin 75 mg/m² resulted in greater incidence and severity of neurotoxicity than the regimen containing cyclophosphamide and cisplatin, 87% (21% severe) versus 52% (2% severe), respectively. The duration of grade III or IV neurotoxicity cannot be determined with precision for the Intergroup study since the resolution dates of adverse events were not collected in the case report forms for this trial and complete follow-up documentation was available only in a minority of these patients. In the GOB (first-line ovarian carcinoma study, neurotoxicity was reported as peripheral neuropathy. The regimen with paclitaxel 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 paclitaxel is given in combination with cisplatin 75 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 paclitaxel 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 paclitaxel. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving paclitaxel 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 paclitaxel administration have been rare (<16%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

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

ilsions, dizziness, and headache have been reported.

Arthralgia/Myalgia

a sistent relationship between dose or schedule of paclitaxel and the frequency myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred 2 or 3 days after paclitaxel administration, and resolved within a few days. The frequency and severify of musculoskeletal symptoms remained unchanged throughout the treatment period.

of paclitaxel 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 paclitaxel was not associated with cumulative hepatic toxicity. Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

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

serum creatinine.

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

Gastrointestinal (GI)

Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients,

lausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients, spectively. These manifestations were usually mild to moderate. Mucositis was schedule ependent 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 nucositis 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.)

AIDS-Helated Kaposi's Sarcoma.)
In the first-line Phase 3 ovarian carcinoma studies, the incidence of nausea and vomiting when If the IniSchiller Trade 3 ovariant carbinoms studies, we included to massed and sometimes probabilities and pacifixed was administered in combination with cisplatin appeared to be greater compared with the database for single-agent paclitaxel in ovarian and breast carcinoma. In addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no

ur any graue was reported more trequently compared to the control arm, but there was no difference for severe diarrhea in these studies. Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, dehydration, esophagitis, constipation, and ascites have been reported. Neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

Injection Site Reaction

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 paclitaxel at different site, ie, "recell," has been reported.
More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis
have been reported. In some cases the onset of the injection site reaction either occurred during
a prolonged infusion or was delayed by a week to 10 days.
A specific treatment for extravasation reactions is unknown at this time. Given the possibility of
extravasation, it is advisable to closely monitor the infusion site for possible infiltration during
drug administration.

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 paclitaxel -related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel 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.

Preparation and Administration Precautions
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. 14 To minimize the risk of dermal exposure,

Skin abnormalities related to radiation recall as well as reports of maculonapular rash. rouritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. In nostmarketing experience, diffuse edema, thickening, and sclerosing of the skin have been eported following paclitaxel administration. Paclitaxel has been reported to exacerbate signs i symptoms of scieroderma. Ports of asthenia and malaise have been received as part of the continuing surveillance of

paclitaxel safety. In the Phase 3 trial of paclitaxel 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/

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.

INCHIUSAGE

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

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 paclitaxel injection solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyplefin) and administration sets.

All patients behald be apprecliated prior to possible visions administration in order to prove the propositions of the proposition of the proposition

administration sets.

All patients should be premedicated prior to paclitaxel injection administration in order to prevent vere hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO Iministered approximately 12 and 6 hours before paclitaxel injection, diphenhydramine (or its

CLINICAL STUDIES: Breast Carcinoma):

1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is paclitaxel injection, at a dose of 175 mg/m² intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used 4 courses of doxorubicin and cyclophosphamide (see CLINICAL STUDIES: Breast Carcinoma).

1) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel injection at a dose of 175 mg/m² administered intravenously over 3 hours event 2 metastatic disease.

of adjuvant chemotherapy, paclitaxel injection at a dose of 175 mg/m² 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

reeks, is paclitaxel injection administered intravenously over 24 hours at a dose of 135 mg/m

For patients with **AIDS-related Kaposi's sarcoma**, paclitaxel injection administered at a dose of 135 mg/m² given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m² given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45-50 mg/m²/ week). In the 2 clinical trials evaluating these schedules (see **CLINICAL STUDIES: AIDS-Related** Kaposi's Sarcoma), the former schedule (135 mg/m² 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/m² every 2 weeks).
Based upon the immunosuppression in patients with advanced HIV disease, the following difications are recommended in these patients: Reduce the dose of dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead

Initiate or repeat treatment with paclitaxel injection only if the neutrophil count is at least

2) Initiate or repeat treatment with pacinaxei injection only if the neuropath count is at least. 1000 cells/mm³;

3) Reduce the dose of subsequent courses of paclitaxel injection by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm³ 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 paclitaxel injection should not be repeated until the neutrophil count is at least 1500 cells/mm³ and the platelet count is at least 100,000 cells/mm³. Paclitaxel Injection should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm³. Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe peripheral neuropathy during paclitaxel injection therapy should have dosage reduced by 20% for subsequent courses of paclitaxel injection. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Hepatic Impairment

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

TABLE 17: RECOMMENDATIONS FOR DOSING IN PATIENTS WITH HEPATIC

IMPAIRMENT BASED ON CLINICAL TRIAL DATA ^a						
Degree of	Recommended Paclitaxel					
Transaminase Levels		Bilirubin Levels ^b	Injection Dose ^c			
	24-hou	ır infusion				
<2 × ULN	and	≤1.5 mg/dL	135 mg/m ²			
2 to <10 × ULN	and	≤1.5 mg/dL	100 mg/m ²			
<10 × ULN	and	1.6-7.5 mg/dL	50 mg/m ²			
≥10 × ULN	or	>7.5 mg/dL	Not recommended			
3-hour infusion						
<10 × ULN	and	≤1.25 × ULN	175 mg/m ²			
<10 × ULN	and	1.26-2.0 × ULN	135 mg/m ²			
<10 × ULN	and	2.01-5.0 × ULN	90 mg/m ²			
≥10 × ULN	or	>5.0 × ULN	Not recommended			
These recommendation	These recommendations are based on dosages for natients without henatic impairment.					

These recommendations are based on dosages for patients without nepatic impairment of 135 mg/m² over 24 hours or 175 mg/m² over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for AIDS-related Kaposi's sarcoma). Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to

differences in clinical trial design Dosage recommendations are for the first course of therapy: further dose reduction in subsequent courses should be based on individual tolerance

Ilways wear impervious gloves when handling vials containing paclitaxel Injection. If paclitaxel njection 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 paclitaxel injection contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea hav

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

Paclitaxel Injection must be diluted prior to infusion. Paclitaxel Injection 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 12 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.

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

Paclitaxel Injection 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 equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel injection, and cimetidine (300 mg) or of paclitaxel injection since they can cause the stopper to collapse resulting in loss of steril

equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel injection, and cimetidine (300 mg) or rantitidine (50 mg) IV 30 to 60 minutes before paclitaxel injection, and cimetidine (300 mg) or rantitidine (50 mg) IV 30 to 60 minutes before paclitaxel injection.

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. Paclitaxel Injection administered intravenously over 3 hours at a dose of 175 mg/m² followed by cisplatin at a dose of 75 mg/m². Or

b. Paclitaxel Injection administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin at a dose of 75 mg/m².

2) In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel injection in the paclitaxel injection administered intravenously over 3 hours every 3 weeks.

For patients with carcinoma of the ovary and the province of the polarity of the paclitaxel injection solution. Chemo Dispensing Pin™ is a trademark of B. Braun Medical Incorporated. Stability

Unopened vials of 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 paclitaxel injection 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 infusion of upon 10 mg/16.7 mL

rrom light. Handling and Disposal See DOSAGE AND ADMINISTRATION: Preparation and Administration Precautions.

REFERENCES

REFERENCES

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