PDR®
54
EDITION
2000

PHYSICIANS' DESK REFERENCE®

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Printed on recycled paper

ISBN: 1-56363-330-2

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 859

100 mg 200 mg 500 mg

1 g 2 g

For injection

Lyophilized Cytoxan®
(cyclophosphamide for injection, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 861

200 mg

300 mg

400 mg

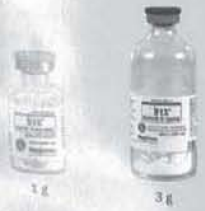
Droxia™
(hydroxyurea capsules, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 863

100 mg
Single-dose vial

Etopophos®
(etoposide phosphate) for Injection

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 866



1 g 3 g

Ifex®
(ifosfamide for injection)

RX BRISTOL-MYERS SQUIBB IMMUNOLOGY P. 868

40 mg/mL

Megace® Oral Suspension
(megestrol acetate)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 870

20 mg 40 mg

Megace®
(megestrol acetate tablets, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 871

1-gm Multi-dose vial

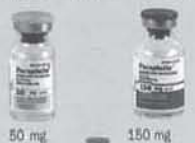
Mesnex®
(mesna) Injection

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 872

40 mg
Also available in 5 mg and 20 mg

Mutamycin®
(mitomycin for injection, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 874



50 mg 150 mg

450 mg

Paraplatin®
(carboplatin for injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 877

50 mg 100 mg

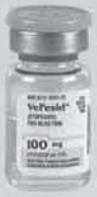
Platinol®-AQ
(cisplatin injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 881

Multi-dose vial
Also available in 30 mg, 100 mg Multi-dose vials

TAXOL®
(paclitaxel) Injection
6 mg/mL

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 888



100 mg
Also available in 150 mg, 500 mg, 1 g

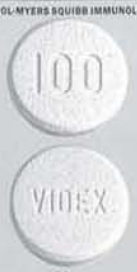
VePesid®

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 888

50 mg

VePesid®
(etoposide) Capsules

RX BRISTOL-MYERS SQUIBB IMMUNOLOGY P. 889



100 mg

Videx®
(didanosine)
Chewable/Dispersible Buffered Tablets

RX BRISTOL-MYERS SQUIBB IMMUNOLOGY P. 895

15 mg 20 mg

30 mg 40 mg

Zerit®
(stavudine) Capsules

RX BRISTOL-MYERS SQUIBB IMMUNOLOGY P. 898

1 mg/mL
200 mL

ZERIT®
(stavudine) for Oral Solution

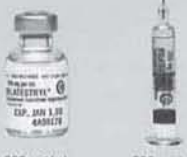
BTG PHARMACEUTICALS

RX BTG PHARMACEUTICALS P. 898

2.5 mg tablets

Oxandrin®
(oxandrolone tablets, USP)

RX BTG PHARMACEUTICALS P. 897



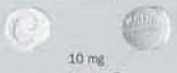
200 mg/mL
5 mL multiple dose vial

200 mg/mL
1 mL unimatic single dose syringe

Delatestryl®

CARNRICK

RX CARNRICK P. 899



10 mg

Amen®
(medroxyprogesterone acetate tablets, USP)

C-III CARNRICK P. 900

35 mg

Bontril® PDM
(phendimetrazine tartrate tablets, USP)

C-III CARNRICK P. 900

105 mg

Bontril® Slow-Release
(phendimetrazine tartrate)

C-V CARNRICK P. 901

Capital® and Codeine Oral Suspension
(acetaminophen, codeine phosphate)
120 mg/5 mL, 12 mg/5 mL

RX CARNRICK P. 901

Exgest® LA
(phenylpropanolamine HCl, guaifenesin)
75 mg / 400 mg

C-III CARNRICK P. 901

Hydrocet®
(hydrocodone bitartrate, USP, acetaminophen, USP)
5 mg / 500 mg

RX CARNRICK P. 902

Midrin®
(isometheptene mucate, USP, dichloralphenazone, USP, acetaminophen, USP)
65 mg / 100 mg / 325 mg

C-IV CARNRICK P. 902

Motofen®
(difenoxin as the HCl, atropine sulfate)
1 mg / 0.025 mg

RX CARNRICK P. 903

375 mg

500 mg

Naprelan®
(naproxen sodium controlled-release tablets)

OTC CARNRICK P. 906

25 mg

Nolahist®

RX CARNRICK P. 906

Nolamine®
(phenylpropanolamine HCl, phenindamine tartrate, chlorpheniramine maleate)
50 mg / 24 mg / 4 mg

RX CARNRICK P. 906

Phrenilin®
(butalbital, USP, acetaminophen, USP)
50 mg / 325 mg

RX CARNRICK P. 906

Phrenilin® Forte
(butalbital, USP, acetaminophen, USP)
50 mg / 650 mg

OTC CARNRICK P. 907

25 mg

Propagest®
(phenylpropanolamine HCl, USP)

RX CARNRICK P. 907

500 mg

750 mg

Saiflex®
(salsalate tablets, USP)

OTC CARNRICK P. 908

Sinulin®
(acetaminophen, USP, chlorpheniramine maleate, USP, phenylpropanolamine HCl, USP)
650 mg / 4 mg / 25 mg

RX CARNRICK P. 909

400 mg

Skelaxin®
(metaxalone)

RX CARNRICK P. 909

100 mg

200 mg

300 mg

Theo-X®
(theophylline extended-release tablets)

CELGENE

RX CELGENE CORPORATION P. 913

50 mg

THALOMID®

Handling and Disposal: Skin reactions associated with doxorubicin have been reported. Skin accidently exposed to doxorubicin should be rinsed copiously with soap and warm water, and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

RUBEX® (doxorubicin hydrochloride for injection, USP) is available as follows:

50 mg —Each single-dose vial contains 50 mg of doxorubicin HCl, USP as a sterile red-orange lyophilized powder, **NDC** 0015-3352-22. Available as one individually cartoned vial.

100 mg —Each single-dose vial contains 100 mg of doxorubicin HCl, USP as a sterile red-orange lyophilized powder, **NDC** 0015-3353-22. Available as one individually cartoned vial.

Storage: Store dry powder at controlled room temperature 15°–30°C (59°–86°F).
The reconstituted solution is stable for 7 days at room temperature or 15 days under refrigeration 2°–8°C (36°–46°F). Protect from exposure to sunlight. Retain in carton until time of use.

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1. Rudolph R, Larson DL: Etiology and Treatment of Chemotherapeutic Agent Extravasation Injuries: A Review. *J Clin Oncol* 1987; 5:1116–1126.
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4. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
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U.S.A.
K9-B001-3-99 3351DIM-06
51-004726-02 Revised: September 1998

TAXOL® ℞ ONLY
{tăx-ol}
(paclitaxel) Injection

WARNING
TAXOL® (paclitaxel) Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%–4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.
TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

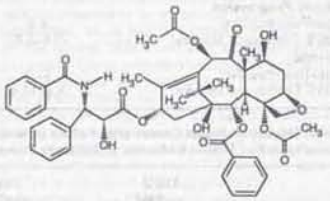
Table 1: Summary of Pharmacokinetic Parameters - Mean Values

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

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

DESCRIPTION

TAXOL® (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.
Paclitaxel is a natural product with antitumor activity. TAXOL is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.
Paclitaxel has the following structural formula:



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

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
Following intravenous administration of TAXOL, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.
Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of TAXOL at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:
[See table 1 above]
It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{max} by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC (0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of TAXOL, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.
The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15–135 mg/m^2 given by 1-hour infusions (n=15), 30–275 mg/m^2 given by 6-hour infusions (n=36), and 200–275 mg/m^2 given by 24-hour infusions (n=54) in Phase 1 & 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of TAXOL in patients with AIDS-related Kaposi's sarcoma have not been studied.
In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicate that between 89%-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.
After intravenous administration of 15–275 mg/m^2 doses of TAXOL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m^2 dose of radiolabeled TAXOL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions** section.) The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.
Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

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

CLINICAL STUDIES

Ovarian Carcinoma:
First-Line Data—The safety and efficacy of TAXOL (paclitaxel) Injection (135 mg/m^2 over 24 hours) in combination with cisplatin (75 mg/m^2) in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in a Phase 3 multicenter, randomized, controlled (vs. cyclophosphamide 750 mg/m^2/cisplatin 75 mg/m^2) clinical trial conducted by the Gynecologic Oncology Group (GOG). A total of 410 patients with Stage III or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) were randomized. Patients treated with TAXOL in combination with cisplatin had significantly longer time to progression (median 16.6 vs. 13.0 months, p=0.0008) and nearly a year longer median survival time (p=0.0002) compared with standard therapy.
[See table 2 at top of next page]
The adverse event profile for patients receiving TAXOL in combination with cisplatin in this study was generally consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 9) and narrative form.
Second-Line Data—Data from five Phase 1 & 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of TAXOL in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% CI: 11% to 37%) and 30% (95% CI: 18% to 46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these two studies measured from the first day of treatment was 7.2 months (range: 3.5–15.8 months) and 7.5 months (range: 5.3–17.4 months), respectively. The median survival was 8.1 months (range: 0.2–36.7 months) and 15.9 months (range: 1.8–34.5+ months).
The Phase 3 study had a bifactorial design and compared the efficacy and safety of TAXOL, administered at two different doses (135 or 175 mg/m^2) and schedules (3- or 24-hour infusion). The overall response rate for the 407 patients was 16.2% (95% CI: 12.8% to 20.2%) with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range: 3.2–21.6 months). Median time to progression was 3.7 months (range 0.1+ – 25.1+ months). Median survival was 11.5 months (range: 0.2-26.3+ months).
Response rates, median survival and median time to progression for the 4 arms are given in the following table.
[See table 3 at top of next page]
Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the two doses (135 or 175 mg/m^2) irrespective of the schedule (3

Continued on next page

Taxol—Cont.

or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m² dose had a response rate similar to that for those receiving the 135 mg/m² dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m² of TAXOL had a longer time to progression than those receiving the 135 mg/m² dose: median 4.2 vs. 3.1 months (p=0.03). The median time to progression for patients receiving the 3-hour vs. the 24-hour infusion was 4.0 months vs. 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 175 mg/m² dose of TAXOL and 11.0 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 TAXOL and 11.2 months for patients receiving the 24-hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

TAXOL remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, a platinum-containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 & 2 clinical studies.

The adverse event profile in this Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 10) and narrative form.

The results of the randomized study support the use of TAXOL (paclitaxel) Injection 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 superior efficacy.

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

Phase 2 open label studies—Two studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. TAXOL was administered in these two trials as a 24-hour infusion at initial doses of 250 mg/m² (with G-CSF support) or 200 mg/m². The response rates were 57% (95% CI: 37% to 75%) and 52% (95% CI: 32% to 72%), respectively. The third Phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of two chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL was 200 mg/m² as a 24-hour infusion with G-CSF support. Nine of the 30 patients achieved a partial response, for a response rate of 30% (95% CI: 15%-50%).

Phase 3 randomized study—This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive TAXOL 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% CI: 22%–30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4–18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03–17.1 months). Median survival was 11.7 months (range: 0–18.9 months).

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

Table 2: Efficacy in the Phase 3 First-Line Ovarian Carcinoma Study

	TAXOL/Cisplatin (n=196)		Cyclophosphamide/Cisplatin (n=214)
• Clinical Response[a]	(n=113)		(n=127)
- rate (percent)	62		48
- p-value		0.04	
• Pathological Response[b]			
- rate (percent)	34		20
- p-value		0.001	
• Pathological Complete Response			
- rate (percent)	21		16
- p-value		0.20	
• Time to Progression			
- median (months)	16.6		13.0
- p-value		0.0008	
• Survival			
- median (months)	35.5		24.2
- p-value		0.0002	

[a] Among evaluable patients only.
[b] Includes patients with pathological complete response plus patients with microscopic residual disease.

Table 3: Efficacy in the Phase 3 Second-Line Ovarian Carcinoma Study

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

Table 4: Efficacy in Breast Cancer after Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Therapy

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

The adverse event profile of the patients who received single-agent TAXOL in the Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events and adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 11) and narrative form.

Non-Small Cell Lung Carcinoma (NSCLC)—In a Phase 3 open label randomized study conducted by the Eastern Cooperative Oncology Group (ECOG), 599 patients were randomized to either TAXOL (T) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², TAXOL (T) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2, and 3 (control).

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

[See table 5 below]

In the ECOG study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had seven subscales that measured subjective assessment of treatment. Of the seven, the Lung Cancer Specific Symptoms subscale favored the TAXOL 135 mg/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 TAXOL in combination with cisplatin in this study was generally consistent with that seen for the pooled analysis of data from 812 patients treated with single-agent TAXOL in 10 clinical studies. These adverse events and adverse events from the Phase 3 first-line NSCLC study are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 12) and narrative form.

AIDS-Related Kaposi's Sarcoma: Data from two Phase 2 open label studies support the use of TAXOL as second-line therapy in patients with AIDS-related Kaposi's sarcoma. Fifty-nine of the 85 patients enrolled in these studies had previously received systemic therapy, including interferon alpha (32%), DaunoXome® (31%), DOXIL® (2%) and doxorubicin containing chemotherapy (42%), with 64% having received prior anthracyclines. Eighty-five percent of the pretreated patients had progressed on, or could not tolerate, prior systemic therapy.

In Study CA139-174 patients received TAXOL at 135 mg/m² as a 3-hour infusion every 3 weeks (intended dose intensity 45 mg/m²/week). If no dose-limiting toxicity was 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 CA139-281 patients received TAXOL (paclitaxel) Injection 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 receiving hematopoietic growth factors before the start of TAXOL therapy, or this support was to be initiated as indicated; the dose of TAXOL was not increased. The dose intensity of TAXOL used in this patient population was lower than the dose intensity recommended for other solid tumors.

DuanoXome® is a registered trademark of NeXstar Pharmaceuticals, Inc. DOXIL® is a registered trademark of Sequus Pharmaceuticals, Inc.

All patients had widespread and poor risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease (T_1), 88% had a CD4 count <200 cells/mm³ (I_1), and 97% had poor risk considering their systemic illness (S_1).

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

Table 5: Efficacy Parameters in the Phase 3 First-Line NSCLC Study

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

[a] Etoposide (VP) 100mg/m² was administered I.V. on days 1, 2 and 3.
[b] Compared to cisplatin/etoposide.

Table 6: 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 two 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 38–39 mg/m²/week in both studies, with a similar range (20–24 to 51–61).

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

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

Table 7: Overall Best Response (Amended ACTG Criteria)

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

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

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

Safety—The adverse event profile of TAXOL administered to patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma was generally similar to that seen in a pooled analysis of data from 812 patients with solid tumors. These adverse events and adverse events from the Phase 2 second-line Kaposi's sarcoma studies are described in the **ADVERSE REACTIONS** section in tabular (Tables 8 and 13) and narrative form. In this immunosuppressed patient population, however, a lower dose intensity of TAXOL and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors.

INDICATIONS

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

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

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

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

CONTRAINDICATIONS

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

TAXOL should not be used in patients with solid tumors who have baseline neutrophil counts of <1500 cells/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%–4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. TAXOL should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³ (<1000 cells/mm³ for patients with KS). Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be retreated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ (>1000 cells/mm³ for patients with KS) and platelets recover to a level >100,000 cells/mm³.

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

Pregnancy: TAXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/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 TAXOL (paclitaxel) Injection is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

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

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

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

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering TAXOL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See **CLINICAL PHARMACOLOGY** section.)

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

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

Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended. For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, TAXOL, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm³.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with TAXOL.

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

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

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

Hepatic: There is evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering TAXOL to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

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

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

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

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

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

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

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

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

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

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies: Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent TAXOL (paclitaxel) Injection. Two hundred and seventy-five patients were treated in eight Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m² administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m²) and two schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m²) administered over 3 hours in a controlled study.

[See table 8 at top of next page]

None of the observed toxicities were clearly influenced by age.

Disease-Specific Adverse Event Experiences First-Line Ovary in Combination: For the 409 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy study, the following table shows the incidence of important adverse events.

[See table 9 on next page]

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

[See table 10 on page 885]

Continued on next page

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