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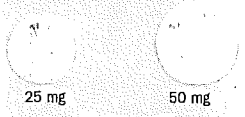
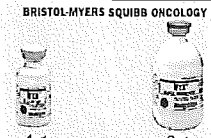
RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 663



25 mg 50 mg

Cytoxan®
(cyclophosphamide tablets, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 665



1 g 3 g

Ifex®
(sterile ifosfamide)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 669

20 mg 40 mg

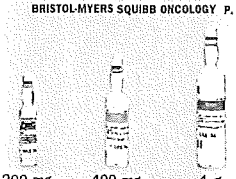
Megace®
(megestrol acetate tablets, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 668

40 mg/mL oral suspension

Megace®
(megestrol acetate)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 670



200 mg 400 mg 1 g

Mesnex®
(mesna injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 671

40 mg
Also available in 5 mg and 20 mg

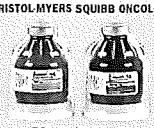
Mutamycin®
(mitomycin for injection, USP)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 673

50 mg 150 mg 450 mg

Paraplatin®
(carboplatin for injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 678



50 mg/100 mg

Platinol®-AQ
(cisplatin for injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 682

Single dose vial

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 686

100 mg

Also available in 150 mg, 500 mg, 1 g

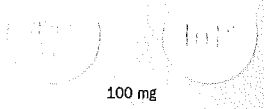
VePesid®
(etoposide for injection)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 686

50 mg

VePesid®
(etoposide)

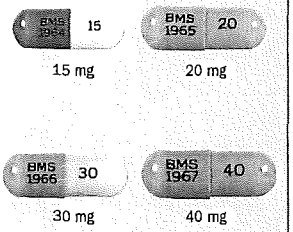
RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 688



100 mg

Videx®
(didanosine)

RX BRISTOL-MYERS SQUIBB ONCOLOGY P. 697



15 mg 20 mg

30 mg 40 mg

Zerit™
(stavudine capsules)

While every effort has been made to reproduce products faithfully, this section is to be considered a quick reference identification aid. In cased of suspected overdosage, etc., chemical analysis of the product should be done.

BURROUGHS WELLCOME

RX BURROUGHS WELLCOME P. 746

2 mg

Alkeran®
(melphalan)

RX BURROUGHS WELLCOME P. 749

10 mg

Cardilate®
(erythrityl tetranitrate)

RX BURROUGHS WELLCOME P. 754

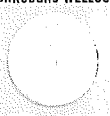
25 mg

C-III BURROUGHS WELLCOME P. 757

325 mg/30 mg

Empirin® with Codeine No.3
(aspirin, codeine phosphate)

C-III BURROUGHS WELLCOME P. 757



325 mg/60 mg

Empirin® with Codeine No.4
(aspirin, codeine phosphate)

RX BURROUGHS WELLCOME P. 762

50 mg

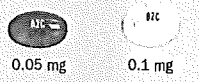
†Imuran®
(azathioprine)

RX BURROUGHS WELLCOME P. 764

5 mg

Kemadrin®
(procyclidine HCl)

RX BURROUGHS WELLCOME P. 765



0.05 mg 0.1 mg

0.2 mg

Lanoxicaps®
(digoxin solution)

RX BURROUGHS WELLCOME P. 776

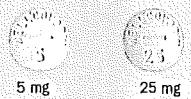
0.125 mg

0.25 mg

0.5 mg

†Lanoxin®
(digoxin)

RX BURROUGHS WELLCOME P. 780



5 mg 25 mg

†Leucovorin Calcium tablets, Wellcovorin® brand
(leucovorin calcium)

RX BURROUGHS WELLCOME P. 781

2 mg

RX BURROUGHS WELLCOME P. 783

250 mg

Mepron®
(atovaquone)

RX BURROUGHS WELLCOME P. 790

2 mg

Myleran®
(busulfan)

RX BURROUGHS WELLCOME P. 799

100 mg 200 mg

Proloprim®
(trimethoprim)

RX BURROUGHS WELLCOME P. 800

50 mg

Purinethol®
(mercaptopurine)

RX BURROUGHS WELLCOME P. 802

100 mg

†Retrovir®
(zidovudine)

RX BURROUGHS WELLCOME P. 810

Semprex™-D
(acrivastine and pseudoephedrine HCl)
8 mg/60 mg

RX BURROUGHS WELLCOME P. 816

†Septra®
(trimethoprim, sulfamethoxazole)
80 mg / 400 mg

RX BURROUGHS WELLCOME P. 816

†Septra® DS
(trimethoprim, sulfamethoxazole)
160 mg / 800 mg

RX BURROUGHS WELLCOME P. 818

40 mg

Thioguanine tablets TABLOID® brand
(thioguanine)

RX BURROUGHS WELLCOME P. 824

75 mg 100 mg

RX BURROUGHS WELLCOME P. 827

200 mg

†Zovirax®
(acyclovir)

RX BURROUGHS WELLCOME P. 827

400 mg

†Zovirax®
(acyclovir)

RX BURROUGHS WELLCOME P. 827

800 mg

†Zovirax®

RX BURROUGHS WELLCOME P. 834

100 mg

300 mg

Zyloprim®
(allopurinol)

CARNRICK

RX CARNRICK P. 839

10 mg

Amen®
(medroxyprogesterone acetate tablets, USP)

C-III CARNRICK P. 841

35 mg

Bontril® PDM
(phendimetrazine tartrate tablets, USP)

C-III CARNRICK P. 841

105 mg

Bontril® Slow-Release
(phendimetrazine tartrate)

CV CARNRICK P. 841

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

RX CARNRICK P. 841

Bristol-Myers Squibb—Cont.

5. Clinical Oncological Society of Australia . Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
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7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033—1049.
8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43:1193—1204.

January 1994 3351DIM-03

TAXOL® ℞

[taks'ŏ l]

(paclitaxel) for Injection Concentrate

WARNING

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

Severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% of patients receiving TAXOL. One of these reactions was fatal in a patient treated without premedication in a Phase 1 study. Patients receiving TAXOL should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists to prevent these reactions. (See "DOSAGE AND ADMINISTRATION" section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

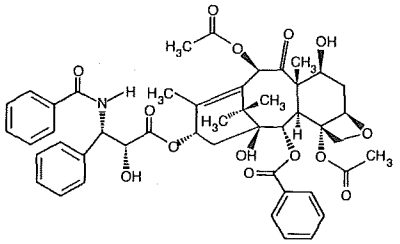
TAXOL therapy should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

DESCRIPTION

TAXOL (paclitaxel) for Injection Concentrate 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) single-dose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Paclitaxel is a natural product with antitumor activity. 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.

Summary of Non-Compartment Pharmacokinetic Parameters
Mean (% Coefficient of Variation) Values by Single-Dose and Infusion

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 (33)	7993 (29)	15.7 (56)	23.8 (35)
135	3	7	2170 (21)	7952 (23)	13.1 (45)	17.7 (20)
175	3	5	3650 (30)	15007 (27)	20.2 (85)	12.2 (25)

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

Key Efficacy Parameters in the Phase 3 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)

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 first table 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 total body clearance and volume of distribution were consistent with the findings in the Phase 3 study.

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.

The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of 15–275 mg/m^2 doses of TAXOL as 1, 6, or 24-hour infusions, mean (SD) values for cumulative urinary recovery of unchanged drug ranged from 1.3% (0.5%) to 12.6% (16.2%) of the dose, indicating extensive non-renal clearance. TAXOL has been demonstrated to be metabolized in the liver in animals and there is evidence suggesting hepatic metabolism in humans. High paclitaxel concentrations have been reported in the bile of patients treated with TAXOL. 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.

CLINICAL STUDIES:

Ovarian Carcinoma: Data from five Phase 1 and 2 clinical studies (189 patients), a multicenter, randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of TAXOL in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% CI = 11–37%) and 30% (95% CI = 18–46%) with a total of six complete and 18 partial responses in 92 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 = 12.8–20.2%), 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. The arms are listed by doses and schedule (mg.m^2/hours). Comparisons between study arms should be done with caution in view of the bifactorial study design and small sample sizes per arm.

[See second table above.]

Analyses were performed as planned by the study protocol, by comparing the two doses (135 or 175 mg/m^2) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose.

Patients receiving the 175 mg/m^2 dose achieved a higher response rate than those receiving the 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3-hour with the 24-hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m^2 dose of TAXOL (paclitaxel) for Injection Concentrate had a longer time to progression than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months (p=0.03). Time to progression was longer for patients receiving the 3-hour vs. the 24-hour infusion: 4.0 months vs. 3.7 months (p=0.08). No difference in survival according to dose or schedule was observed.

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

The adverse event profile in the Phase 3 study was consistent with that seen for a pooled analysis performed on 812 patients treated in ten clinical studies (see, "ADVERSE REACTIONS" section). For the 403 patients who received TAXOL in the Phase 3 study, the following table shows the incidence of some key adverse events by treatment arm. The arms are listed by dose and schedule (mg/m^2/hours).

[See first table on top of next page.]

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. Additionally, peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

The results of the randomized study support the use of TAXOL at doses of 135 or 175 mg/m^2, administered by a 3-hour infusion. The same doses administered by 24-hour infusion were more toxic; the bifactorial study design and small sample size per arm preclude definitive conclusions regarding relative efficacy between the 4 arms of the study

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 2 trials as a 24-hour infusion at initial doses of 250 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response rates were 57% (95% Cl: 37–75%) and 52% (95% Cl: 32–72%), respectively. The third phase 2 study evaluated quality of life changes and was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of TAXOL was 200 mg/m^2 as a 24-hour infusion with G-CSF support. Nine of the 30 patients analyzed 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 one or two regimens of chemotherapy. Patients were randomized to received TAXOL at a dose of either 175 mg/m^2 or 135 mg/m^2 given as a 3-hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% Cl: 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. The arms are listed by dose and schedule (mg•m^2/hours).

[See second table at right.]

For the 458 patients who received TAXOL (paclitaxol) for Injection Concentrate in the Phase 3 study, the following table shows the incidence of some key adverse events by treatment arm (each arm was administered by a 3-hour infusion).

[See third table at right.]

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

INDICATIONS

TAXOL is indicated, after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

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.

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 baseline neutropenia of <1,500 cells/mm^3.

WARNINGS

Patients should be pretreated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine) before receiving TAXOL. (See "DOSAGE AND ADMINISTRATION" section.) Severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% of patients receiving TAXOL. These reactions are probably histamine-mediated. One of these reactions was fatal in a patient with pulmonary metastases who was a participant in a Phase I trial. This patient received no premedication; the first course of TAXOL, which was uneventful, was administered at 190 mg/m^2 infused over three hours. Within a few minutes from the beginning of a second course of TAXOL, the patient developed severe hypotension and died. 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 in patients with baseline neutrophil counts of less than 1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1,500 cells/

Frequency of Key Adverse Events in the Phase 3 Ovarian Carcinoma Study

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

* *All patients received premedication*

Key Efficacy Parameters in the Phase 3 Breast Carcinoma Study

	175/3 (n=235)	135/3 (n=236)
• **Response**		
–rate (percent)	28	22
–95% Confidence Interval	(22–34)	(17–27)
• **Time to Progression**		
–median (months)	4.2	3.0
–95% Confidence Interval	(3.2–4.6)	(2.5–3.8)
• **Survival**		
–median (months)	11.7	10.5
–95% Confidence Interval	(10.0–13.8)	(9.0–12.8)

Frequency of Key Adverse Events in the Phase 3 Breast Carcinoma Study

		Percent of Patients	
		175 mg/m^2 (n=229)	135 mg/m^2 (n=229)
• **Bone Marrow**			
–Neutropenia*	<2,000/mm^3	90	81
	<500/mm^2	28	19
Thrombocytopenia*	<100,000/mm^2	11	7
	<50,000/mm^2	3	2
–Anemia*	<11 g/dL	55	47
	<8 g/dL	4	2
–Infections		23	15
–Febrile Neutropenia		2	2
• **Hypersensitivity Reaction****			
–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*

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.

TAXOL may cause fetal harm when administered to a pregnant woman. TAXOL has been shown to be embryo- and fetotoxic in rats and rabbits and to decrease fertility in rats. In these studies, TAXOL was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorptions and embryo-fetal deaths. No gross external, soft tissue or skeletal alterations occurred. There are no studies in pregnant women. If TAXOL is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOL.

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], 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 Interaction: In a Phase I trial[1] using escalating doses of TAXOL (110–200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (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.

Based on *in vitro* data, there is the possibility of an inhibition of TAXOL metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with TAXOL when they are receiving ketoconazole as concomitant therapy.

Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxic-

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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 > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. In the case of severe neutropenia (< 500 cells/mm^3 for seven days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

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, angiodema 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 and bradycardia have been observed during administration of TAXOL, but generally do not require treatment. 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.

Hepatic: There is no evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes, but no data are available for patients with severe baseline cholestasis. However, evidence suggests that the liver plays an important role in the metabolism of TAXOL. As a result, since there are no data available from patients with severe liver disease, caution should be exercised when administering TAXOL to patients with severe hepatic impairment.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of TAXOL has not been studied. TAXOL has been shown to be mutagenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice) mammalian test systems, however, it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assay. TAXOL at an I.V. dose of 1 mg/kg (6 mg/m^2) produced low fertility and fetal toxicity in rats. TAXOL has also been shown to be maternal and embryo-fetal toxic in rabbits receiving the drug at an I.V. dose of 3 mg/kg (33 mg/m^2) during organogenesis. (See "WARNINGS" section.)

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

Nursing Mothers: It is not known whether the drug is excreted in human milk. 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 children have not been established.

ADVERSE REACTIONS

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. Two hundred and seventy-five patients were treated in 8 Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m^2 administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoletic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m^2) administered over 3 hours in a controlled study. [See table above.]

Summary of Adverse Events in 812 Patients Receiving TAXOL

	% Incidence
• **Bone Marrow**	
—Neutropenia <2,000/mm^3	90
< 500/mm^3	52
—Leukopenia <4,000/mm^3	90
<1,000/mm^3	17
—Thrombocytopenia <100,000/mm^3	20
< 50,000/mm^3	7
—Anemia <11 g/dL	78
< 8 g/dL	16
—Infections	30
—Bleeding	14
—Red Cell Transfusions	25
—Platelet Transfusions	2
• **Hypersensitivity Reaction***	
—All	41
—Severe	2
• **Cardiovascular**	
—Vital Sign Changes**	
—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

* *All patients received premedication*
** *During the first 3-hours of infusion*
None of the observed toxicities were clearly influenced by age.

The following data relate to the overall safety database of 812 patients treated in clinical studies. In addition, rare events have been reported from the postmarketing experience or from other clinical studies. The frequency and severity of adverse events are generally similar between patients receiving TAXOL for the treatment of ovarian or breast carcinoma. The frequency and severity of key adverse events for the Phase 3 ovarian and breast carcinoma studies are presented in tabular form by treatment arm in "CLINICAL

portant hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in Phase 3 ovarian study with a 3-hour infusion, neutrophil counts decline below 500 cells/mm^3 in 13% of the patients treated with a dose of 135mg/m^2 compared to 27% at a dose of 175 mg/m^2(p=0.05). In the same study, severe neutropenia (< 500 cells/mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

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 ovarian study, infectious episodes were reported in 19% of the patients given either 135 or 175 mg/m^3 dose by a 3 hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Thrombocytopenia was uncommon, and almost never severe (< 50,000 cells/mm^3). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count < 50,000 cells/mm^3 at the time of their worst nadir. Among the 812 patients, bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. In the Phase 3 ovarian study, bleeding episodes were reported in 10% of the patients receiving either the 135 or 175 mg/m^2 dose given by a 3-hour infusion; no patients treated with the 3-hour infusion received platelet transfusions.

Anemia (Hb < 11 g/dL) was observed in 78% of all patients and was severe (Hb < 8g/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% become anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received

or schedule of TAXOL administration. In the Phase 3 ovarian study the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of TAXOL (paclitaxel) for injection Concentrate infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia. The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Cardiovascular: Hypotension, during the first 3-hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3-hours of infusion, occurred in 3% of all patients and 1% of all courses. In Phase 3 ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to TAXOL occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with TAXOL at 175 mg/m^2 over 24-hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported

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