Mead Johnson
ONCOLOGY PRODUCTS 2/10/00

L Only

TAXOL7 (paclitaxel) INJECTION

WARNING

TAXOL**7** (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteriods, 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 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

DESCRIPTION

TAXOL (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor**7** EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

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

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*Cremophor**7** EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor**7** EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Paclitaxel has the following structural formula:

(SEE CURRENTLY APPROVED PACKAGE INSERT)

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

CLINICAL PHARMACOLOGY

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

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

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

TABLE 1
SUMMARY OF PHARMACOKINETIC PARAMETERS - MEAN VALUES

Dose (mg/m^2)	Infusion Duration (h)	N (patients)	C_{MAX} (ng/mL)	AUC(0-4) (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(0-4) = Area under the plasma concentration-time curve from time 0 to infinity
CL_T = Total body clearance

It appeared that with the 24-hour infusion of TAXOL, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{MAX} by 87%, whereas the AUC(0-4) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{MAX} and AUC(0-4) 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 g/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 6 -hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6 ,3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 -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, 17 -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 -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.

CLINICAL STUDIES

Ovarian Carcinoma

First-Line Data: The safety and efficacy of TAXOL followed by cisplatin in patients with advanced ovarian cancer and no prior chemotherapy were evaluated in two Phase 3 multicenter, randomized, controlled trials. In an Intergroup study led by the European Organization for Research and Treatment of Cancer involving the Scandinavian Group NOCOVA, the National Cancer Institute of Canada, and the Scottish Group, 680 patients with Stage II$_{B-C}$, III, or IV disease (optimally or non-optimally debulked) received either TAXOL 175 mg/m^2 infused over 3 hours followed by cisplatin 75 mg/m^2 (Tc) or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 (Cc) for a median of six courses. Although the protocol allowed further therapy, only 15% received both drugs for 9 or more courses. In a study conducted by the Gynecological Oncology Group (GOG), 410 patients with Stage III or IV disease (>1 cm residual disease after staging laparotomy or distant metastases) received either

TAXOL 135 mg/m^2 infused over 24 hours followed by cisplatin 75 mg/m^2 or cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 for six courses.

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

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

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

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

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

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

---p-value[c]	0.0016
---hazard ratio[c]	0.73
---95% CI[c]	0.60 – 0.89

[a] TAXOL dose in mg/m^2/infusion duration in hours; cyclophosphamide and cisplatin doses in mg/m^2.
[b] Among patients with measurable disease only.
[c] Unstratified.

FIGURE 1
SURVIVAL: Cc VERSUS Tc (INTERGROUP)

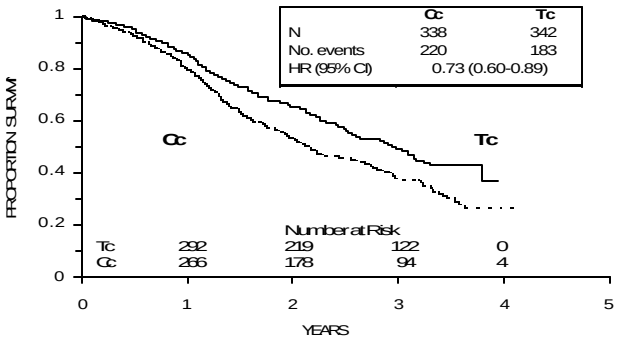

FIGURE 2
SURVIVAL: Cc VERSUS Tc (GOG-111)

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