

PRODUCT MONOGRAPH

PACLITAXEL FOR INJECTION

6 mg/mL

ANTINEOPLASTIC AGENT

Manufacturer:
IVAX Pharmaceuticals Inc.
4400 Biscayne Blvd.,
Miami, Florida, USA
33137

Distributed by:
IVAX Pharmaceuticals Canada Inc.
1 Place Ville-Marie, Suite 3900
Montreal, Quebec, Canada
H3B 4M7

Date of Preparation:
April 1998

Date of Revision:
December 20, 2005

Control #102197

PRODUCT MONOGRAPH
PACLITAXEL FOR INJECTION

6 mg/mL

THERAPEUTIC CLASSIFICATION

ANTINEOPLASTIC AGENT

PACLITAXEL FOR INJECTION SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPEUTIC AGENTS.

PATIENTS RECEIVING PACLITAXEL FOR INJECTION SHOULD BE PRETREATED WITH CORTICOSTEROIDS, ANTIHISTAMINES, AND H₂ ANTAGONISTS (SUCH AS DEXAMETHASONE, DIPHENHYDRAMINE AND CIMETIDINE OR RANITIDINE) TO MINIMIZE HYPERSENSITIVITY REACTIONS (SEE DOSAGE AND ADMINISTRATION). ALL CLINICAL STUDIES REFERRED TO IN THIS PRODUCT MONOGRAPH WERE CONDUCTED USING TAXOL® PACLITAXEL. SEVERE HYPERSENSITIVITY REACTIONS CHARACTERIZED BY DYSPNEA AND HYPOTENSION REQUIRING TREATMENT, ANGIOEDEMA, AND GENERALIZED URTICARIA HAVE OCCURRED IN PATIENTS RECEIVING PACLITAXEL FOR INJECTION. THESE REACTIONS ARE PROBABLY HISTAMINE MEDIATED. RARE FATAL REACTIONS HAVE OCCURRED IN PATIENTS DESPITE PRE-TREATMENT. PATIENTS WHO EXPERIENCE SEVERE HYPERSENSITIVITY REACTIONS TO PACLITAXEL FOR INJECTION SHOULD NOT BE RECHALLENGED WITH THE DRUG.

ACTIONS AND CLINICAL PHARMACOLOGY

PACLITAXEL FOR INJECTION is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization.

In vitro, PACLITAXEL FOR INJECTION exhibits cytotoxic activity against a wide variety of both human and rodent tumor cell lines including leukemia, non-small cell lung carcinoma, small cell lung carcinoma, colon carcinoma, CNS carcinoma, melanoma, renal carcinoma, ovarian carcinoma and breast carcinoma (see PHARMACOLOGY).

The pharmacokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m², and infusion schedules ranging from 3 to 24 hours. Following intravenous administration of PACLITAXEL FOR INJECTION, the drug exhibited a biphasic decline in plasma concentrations. 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. In patients treated with doses of 135 and 175 mg/m² given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3.0 to 52.7 hours, and total body clearance has ranged from 11.6 to 24.0 L/h/m². Mean steady state volume of distribution has ranged from 198 to 688 L/m², indicating extensive extravascular distribution and/or tissue binding.

Following 3 hour infusions of 175 mg/m², mean terminal half-life was estimated to be 9.9 hours;

mean total body clearance was 12.4 L/h/m².

Variability in systemic paclitaxel exposure, as measured by AUC_{0-∞} for successive treatment courses was minimal; there was no evidence of accumulation of paclitaxel with multiple treatment courses.

The pharmacokinetics of paclitaxel have been shown to be non-linear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose-related decrease in total body clearance. These findings are most readily observed in patients in whom high plasma concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicated that on average 89% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

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 (see PRECAUTIONS: Drug Interactions). The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of PACLITAXEL FOR INJECTION, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.7% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m² dose of radiolabeled PACLITAXEL FOR INJECTION as a 3-hour infusion, 14% of the radioactivity was recovered in the urine and 71% was excreted in the feces in 120 hours. 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.

INDICATIONS AND CLINICAL USE

PACLITAXEL FOR INJECTION is indicated, alone or in combination, for the treatment of carcinoma of the ovary, breast, lung, or AIDS-related Kaposi's Sarcoma.

Ovarian Carcinoma

- First-line treatment in combination with other chemotherapeutic agents.
- Second-line treatment of metastatic carcinoma of the ovary after failure of standard therapy.

Breast Carcinoma

- Adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-

negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. (See PHARMACOLOGY - Clinical Trials).

- Second-line treatment of metastatic carcinoma of the breast after failure of standard therapy.

Lung Carcinoma

- First-line treatment of advanced non-small cell lung cancer.

Kaposi's Sarcoma

- Treatment of advanced, liposomal anthracycline-refractory AIDS-related Kaposi's Sarcoma.

CONTRAINDICATIONS

PACLITAXEL FOR INJECTION is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in polyethoxylated castor oil.

PACLITAXEL FOR INJECTION should not be used in patients with severe baseline neutropenia ($<1,500$ cells/mm³) nor in patients with AIDS-related Kaposi's Sarcoma with baseline or subsequent neutrophil counts of $<1,000$ cells/mm³.

WARNINGS

PACLITAXEL FOR INJECTION should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

PACLITAXEL FOR INJECTION should be administered as a diluted infusion. Patients receiving PACLITAXEL FOR INJECTION should be pretreated with corticosteroids, antihistamines, and H₂ antagonists (such as dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions (see DOSAGE AND ADMINISTRATION). Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, or generalized urticaria have occurred in approximately 2% of patients receiving PACLITAXEL FOR INJECTION. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pre-treatment. In case of a severe hypersensitivity reaction, PACLITAXEL FOR INJECTION infusion should be discontinued immediately and the patient should not be rechallenged with the drug (see ADVERSE REACTIONS).

PACLITAXEL FOR INJECTION should not be administered to patients with baseline neutrophil counts of less than 1 500 cells/mm³ ($<1,000$ cells/mm³ for patients with Kaposi's Sarcoma). Bone marrow suppression (primarily neutropenia) is dose and schedule dependent and is the dose-limiting toxicity within a regimen. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted during PACLITAXEL FOR INJECTION treatment. Patients should not be retreated with subsequent cycles of PACLITAXEL FOR INJECTION until neutrophils recover to a level $>1,500$ cells/mm³ ($>1,000$ cells/mm³ for patients with Kaposi's Sarcoma) and platelets recover to a level $>100,000$ cells/mm³ (see DOSAGE AND ADMINISTRATION).

Severe cardiac conduction abnormalities have been reported in < 1% of patients during PACLITAXEL FOR INJECTION therapy. If patients develop significant conduction abnormalities during administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with PACLITAXEL FOR INJECTION (see ADVERSE REACTIONS).

Use in Pregnancy

PACLITAXEL FOR INJECTION may cause fetal harm when administered to a pregnant woman. PACLITAXEL FOR INJECTION has been shown to be embryotoxic and fetotoxic in rabbits and to decrease fertility in rats. There are no studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with PACLITAXEL FOR INJECTION. If PACLITAXEL FOR INJECTION is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard.

Nursing Mothers

It is not known whether PACLITAXEL FOR INJECTION is excreted in human milk. Breast feeding should be discontinued for the duration of PACLITAXEL FOR INJECTION therapy.

Use in Children

The safety and effectiveness of PACLITAXEL FOR INJECTION 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 PACLITAXEL FOR INJECTION 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 PACLITAXEL FOR INJECTION 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 PACLITAXEL FOR INJECTION for use in this population.

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 PACLITAXEL FOR INJECTION solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Drug Interactions

Cisplatin

In a Phase I trial in which PACLITAXEL FOR INJECTION was administered as a 24-hour infusion and cisplatin was administered as a 1 mg/min infusion, myelosuppression was more profound when PACLITAXEL FOR INJECTION was given after cisplatin than with the alternate sequence (i.e. PACLITAXEL FOR INJECTION before cisplatin). When PACLITAXEL FOR INJECTION is given before cisplatin, the safety profile of PACLITAXEL FOR INJECTION is consistent with that reported for single-agent use. Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when PACLITAXEL FOR INJECTION was administered following cisplatin. Therefore, PACLITAXEL FOR INJECTION should be given before cisplatin when used in combination.

Cimetidine

The effect of cimetidine premedication on the metabolism of paclitaxel has been investigated; the clearance of paclitaxel was not affected by cimetidine pretreatment.

Montelukast

In recent publications, it was reported that montelukast (Singulair®) is a potent *in vitro* inhibitor of the cytochrome P450 2C8 enzyme and therefore has the potential for drug interactions with substrates of this pathway. Concomitant administration of montelukast has the potential to decrease the metabolic clearance of drugs that are primarily metabolized by CYP 2C8 (or possessing CYP-2C8-catalyzed metabolism as a major clearance pathway) which may result in an increase in plasma concentrations of these drugs (or thereby eliciting pharmacokinetic drug-drug interactions).

Substrates, Inducers, Inhibitors of Cytochrome P450 2C8 and 3A4

The metabolism of PACLITAXEL FOR INJECTION is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering PACLITAXEL FOR INJECTION concomitantly with known substrates, inducers or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -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.

Potential interactions between PACLITAXEL FOR INJECTION, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials. Caution and close monitoring of liver function is required; further, no unapproved (e.g., investigational) protease inhibitor should be administered with PACLITAXEL FOR INJECTION.

Doxorubicin

Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of PACLITAXEL FOR INJECTION and doxorubicin when PACLITAXEL FOR INJECTION was administered BEFORE doxorubicin and using longer than

recommended infusion times (PACLITAXEL FOR INJECTION administered over 24 hours; doxorubicin administered over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when PACLITAXEL FOR INJECTION and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and 3-hour PACLITAXEL FOR INJECTION infusion found no sequence effects on the pattern of toxicity.

Hematology

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

Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL should not be treated with PACLITAXEL FOR INJECTION (see WARNINGS, CONTRAINDICATIONS). 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 PACLITAXEL FOR INJECTION and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with PACLITAXEL FOR INJECTION.

Cardiovascular

Hypotension, hypertension and bradycardia have been observed during PACLITAXEL FOR INJECTION administration; patients are usually asymptomatic and generally do not require treatment. In severe cases, PACLITAXEL FOR INJECTION infusions may need to be interrupted or discontinued at the discretion of the treating physician. Frequent monitoring of vital signs, particularly during the first hour of PACLITAXEL FOR INJECTION infusion, is recommended. Continuous cardiac monitoring is not required except for patients who develop serious conduction abnormalities (see WARNINGS, ADVERSE REACTIONS).

Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual. A dose reduction of 20% is recommended for all subsequent courses of PACLITAXEL FOR INJECTION for severe neuropathy (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

PACLITAXEL FOR INJECTION contains dehydrated ethanol, 396 mg/mL; consideration should be given to possible CNS and other effects of ethanol. Children may be more sensitive than the adults to the effects of ethanol (see WARNINGS; Use in Children).

Hepatic

There is evidence that the toxicity of PACLITAXEL FOR INJECTION is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering PACLITAXEL FOR INJECTION to patients with moderate to severe hepatic impairment and dose adjustments should be considered (see ADVERSE REACTIONS).

Injection Site Reaction

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

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of PACLITAXEL FOR INJECTION 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.

Driving/Operating Machinery

Since PACLITAXEL FOR INJECTION contains ethanol, consideration should be given to the possibility of CNS and other effects.

ADVERSE REACTIONS

The frequency and severity of adverse events are generally similar between patients receiving PACLITAXEL FOR INJECTION for the treatment of ovarian, breast non-small cell lung carcinoma, or Kaposi's Sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See CLINICAL TRIALS: AIDS-Related Kaposi's Sarcoma).

The incidences of adverse reactions in the table that follows are derived from ten clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated with single-agent PACLITAXEL FOR INJECTION at doses ranging from 135-300 mg/m²/day and schedules of 3 or 24 hours. Data from a subset of 181 patients treated at the recommended dose of 175 mg/m² and a 3-hour infusion schedule is also included in the table.

	135-300 mg/m² % of Patients N=812	175 mg/m² % of Patients N=181
<u>Bone Marrow</u>		
Neutropenia < 2,000/mm ³	90	87
< 500/mm ³	52	27
Leukopenia < 4,000/mm ³	90	86
< 1,000/mm ³	17	4
Thrombocytopenia < 100,000/mm ³	20	6
< 50,000/mm ³	7	1
Anemia < 11 g/dL	78	62
< 8 g/dL	16	6
Infections	30	18
Bleeding	14	9
Red Cell Transfusions	25	13
Red Cell Transfusions (normal baseline)	12	6
Platelet Transfusions	2	0
<u>Hypersensitivity Reactions</u>		
All	41	40
Severe	2	1
<u>Cardiovascular</u>		
Bradycardia (first 3 hours of infusion)	3	3
Hypotension (first 3 hours of infusion)	12	11
Severe events	1	2
<u>Abnormal ECG</u>		
All Patients	23	13
Patients with normal baseline	14	8
<u>Peripheral Neuropathy</u>		
Any symptoms	60	64
Severe symptoms	3	4
<u>Myalgia/Arthralgia</u>		
Any symptoms	60	54
Severe symptoms	8	12
<u>Gastrointestinal</u>		
Nausea and vomiting	52	44
Diarrhea	38	25
Mucositis	31	20
<u>Alopecia</u>		
	87	93
<u>Hepatic (Patients with normal baseline)</u>		
Bilirubin elevations	7	4
Alkaline phosphatase elevations	22	18
AST elevations	19	18
<u>Injection site reactions</u>		
	13	4

Safety referring to a large randomized trial of PACLITAXEL FOR INJECTION (135 mg/m² over 24 hours) / cisplatin (75 mg/m²) versus cyclophosphamide/cisplatin, including 410 patients (196 receiving PACLITAXEL FOR INJECTION), has been evaluated. The combination of PACLITAXEL FOR INJECTION with platinum agents has not resulted in any clinically relevant changes to the safety profile of the drug when used at the recommended dosage.

Safety data were collected for 3,121 patients in the Phase III adjuvant breast carcinoma study. The adverse event profile for the patients who received PACLITAXEL FOR INJECTION subsequent to cyclophosphamide and doxorubicin was consistent with that seen in the pooled analysis of data from 812 patients treated with single-agent PACLITAXEL FOR INJECTION in 10 clinical studies.

SUMMARY OF 3-HOUR INFUSION DATA AT A DOSE OF 175 mg/m²

Unless otherwise stated, the following safety data relate to 62 patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m² and a 3-hour infusion schedule, in phase III clinical trials. All patients were premedicated to minimize hypersensitivity reactions. Data from these clinical trials demonstrate that PACLITAXEL FOR INJECTION given at this dose and schedule is well tolerated. Bone marrow suppression and peripheral neuropathy were the principle dose-related adverse effects associated with PACLITAXEL FOR INJECTION. Compared to 24-hour infusion schedules, neutropenia was less common when PACLITAXEL FOR INJECTION was given as a 3-hour infusion. Neutropenia was generally rapidly reversible and did not worsen with cumulative exposure. The frequency of neurologic symptoms increases with repeated exposure.

None of the observed toxicities were influenced by age.

AIDS-related KAPOSÍ'S SARCOMA

The following table shows the frequency of important adverse events in the 85 patients with KS treated with two different single-agent PACLITAXEL FOR INJECTION regimens.

Frequency^a of Important* Adverse Events in the AIDS-Related Kaposi's Sarcoma Studies

	Percent of Patients	
	Study CA139-174 135/3 ^b /3 wk (n = 29)	Study CA139-281 100/3 ^b /2 wk (n = 56)
<u>Bone Marrow</u>		
Neutropenia < 2,000/mm ³	100	95
< 500/mm ³	76	35
Thrombocytopenia < 100,000/mm ³	52	27
< 50,000/mm ³	17	5
Anemia < 11 g/dL	86	73
< 8 g/dL	34	25
Febrile Neutropenia	55	9
<u>Opportunistic Infections</u>		
Any	76	54
Cytomegalovirus	45	27
Herpes Simplex	38	11
<i>Pneumocystis carinii</i>	14	21
<i>M. avium intracellulare</i>	24	4
Candidiasis, esophageal	7	9
Cryptosporidiosis	7	7
Cryptococcal meningitis	3	2
Leukoencephalopathy	—	2
<u>Hypersensitivity Reaction^c</u>		
All	14	9
<u>Cardiovascular</u>		
Hypotension	17	9
Bradycardia	3	—
<u>Peripheral Neuropathy</u>		
Any	79	46
Severe**	14	16
<u>Myalgia/Arthralgia</u>		
Any	93	48
Severe**	14	16
<u>Gastrointestinal</u>		
Nausea and vomiting	69	70

	Percent of Patients	
	Study CA139-174 135/3 ^b /3 wk (n = 29)	Study CA139-281 100/3 ^b /2 wk (n = 56)
Diarrhea	90	73
Mucositis	45	20
Renal (Creatinine elevation)		
Any	34	18
Severe**	7	5
Discontinuation for drug toxicity	7	16

^a Based on worst course analysis.

^b PACLITAXEL FOR INJECTION dose in mg/m²/infusion duration in hours.

^c All patients received premedication.

* Clinically relevant and/or possibly related.

** Severe events are defined as at least Grade III toxicity.

As demonstrated in the above table, toxicity was more pronounced in the study utilizing PACLITAXEL FOR INJECTION at a dose of 135 mg/m² every 3 weeks than in the study utilizing PACLITAXEL FOR INJECTION at a dose of 100 mg/m² every 2 weeks. Notably, severe neutropenia (76% versus 35%), febrile neutropenia (55% versus 9%), and opportunistic infections (76% versus 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described below, should be taken into account. (See CLINICAL TRIALS: AIDS-Related Kaposi's Sarcoma).

Adverse Experiences by Body System

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent PACLITAXEL FOR INJECTION in 10 clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received PACLITAXEL FOR INJECTION in combination with cisplatin or in patients with breast cancer who received PACLITAXEL FOR INJECTION after doxorubicin/cyclophosphamide in the adjuvant setting, or in patients with AIDS-related Kaposi's sarcoma, and that occurred with a difference that was clinically significant in these populations are also described. In addition, rare events have been reported from postmarketing experience or from other clinical studies.

The frequency and severity of adverse events have been generally similar for all patients receiving PACLITAXEL FOR INJECTION. However, patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described.

Hematologic

The most frequent significant undesirable effect of PACLITAXEL FOR INJECTION was bone marrow suppression. Neutropenia was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (<500 cells/mm³) occurred in 27% of patients treated at a dose of 175 mg/m², but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days or more. Neutropenia was not more frequent or severe in patients who received prior radiation therapy, nor did it appear to be affected by treatment duration or cumulative exposure.

When PACLITAXEL FOR INJECTION was administered to patients with ovarian carcinoma at a dose of 175 mg/m²/3 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of severe neutropenia and of febrile neutropenia were similar in the PACLITAXEL FOR INJECTION plus cisplatin arm and in the control arm.

When PACLITAXEL FOR INJECTION was administered in combination with cisplatin to patients with advanced NSCLC in the Eastern Cooperative Oncology Group (ECOG) study, the incidence of neutropenia (Grade IV) was 74% (PACLITAXEL FOR INJECTION 135 mg/m²/24 hours plus cisplatin) and 65% (PACLITAXEL FOR INJECTION 250 mg/m²/24 hours plus cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide. Considerably less Grade IV neutropenia was observed in the European Organization for Research and Treatment of Cancer (EORTC) (28%) and CA139-208 (45%) studies for PACLITAXEL FOR INJECTION 175 mg/m²/3 hours plus cisplatin (without G-CSF).

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% of the patients given 135 mg/m² and 26% of the patients given 175 mg/m² by a 3-hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See DOSAGE AND ADMINISTRATION).

Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count $< 50,000$ cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the PACLITAXEL FOR INJECTION dose and schedule. In the Phase III second-line ovarian cancer study, bleeding episodes were reported in 10% of the patients who received study medication; however, none of the patients treated with the 3-hour infusion received platelet transfusions. In the adjuvant breast carcinoma trial, the incidence of severe thrombocytopenia and platelet transfusions increased with higher doses of doxorubicin.

Anemia (Hb <11 g/dL) was observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12%

of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSR)

All patients received premedication prior to PACLITAXEL FOR INJECTION (see WARNINGS section). The frequency and severity of HSR were not affected by the dose or schedule of PACLITAXEL FOR INJECTION administration. In the Phase III second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSR when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of PACLITAXEL FOR INJECTION infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

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

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

Cardiovascular

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

Significant cardiovascular events possibly related to single-agent PACLITAXEL FOR INJECTION occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with PACLITAXEL FOR INJECTION at 175 mg/m² over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement. The incidence of Grade III or greater cardiovascular events was 13% (PACLITAXEL FOR INJECTION 135 mg/m²/24 hours plus cisplatin), 12% (PACLITAXEL FOR INJECTION 250 mg/m²/24 hours plus cisplatin and G-CSF), and 6% (PACLITAXEL FOR INJECTION 175 mg/m²/3 hours plus cisplatin) when PACLITAXEL FOR INJECTION followed by cisplatin was administered to patients with advanced NSCLC; there was a similar incidence in the non-PACLITAXEL FOR INJECTION control arms. The apparent increase in these cardiovascular events in patients with NSCLC compared to patients with breast or ovarian cancer is possibly related to the difference in cardiovascular risk factors among patients with lung cancer.

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

most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECG at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See PRECAUTIONS: Drug Interactions)

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

Respiratory

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

Neurologic

The frequency and severity of neurologic manifestations were influenced by prior and concomitant therapy with cisplatin. In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent PACLITAXEL FOR INJECTION. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy.

The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34-51% from course 2 to 10. Peripheral neuropathy was the cause of PACLITAXEL FOR INJECTION discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of PACLITAXEL FOR INJECTION discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for PACLITAXEL FOR INJECTION therapy. In the Intergroup first-line ovarian carcinoma study, the regimen with PACLITAXEL FOR INJECTION 175 mg/m² by 3-hour infusion followed by cisplatin 75 mg/m² resulted in greater incidence and severity of neurotoxicity (reported as neuromotor or neurosensory events) than the regimen containing cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m², 87% (21% severe) versus 52% (2% severe), respectively. In the GOG first-line ovarian carcinoma study, the regimen with PACLITAXEL FOR INJECTION (135 mg/m² over 24 hours) followed by cisplatin (75 mg/m²) resulted in an incidence of neurotoxicity (reported as peripheral neuropathy) that was similar to the regimen containing cyclophosphamide 750 mg/m² followed by cisplatin 75 mg/m², 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in Intergroup and GOG trials suggests that when PACLITAXEL FOR INJECTION is given in combinations with cisplatin 75 mg/m², the incidence of severe neurotoxicity is more common at a PACLITAXEL FOR INJECTION dose of 175 mg/m² given by 3-hour infusion (21%) than at a dose of 135 mg/m² given by 24-hour infusion (3%). In patients with NSCLC, administration of PACLITAXEL FOR INJECTION followed by cisplatin resulted in greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent PACLITAXEL FOR INJECTION. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving PACLITAXEL FOR INJECTION 135 mg/m² by 24-hour infusion

followed by cisplatin 75 mg/m² and 8% of NSCLC patients receiving cisplatin/etoposide.

Other than peripheral neuropathy, serious neurologic events following PACLITAXEL FOR INJECTION administration have been rare (<1%) and have included grand mal seizures, ataxia and encephalopathy.

Rare reports of autonomic neuropathy resulting in paralytic ileus and motor neuropathy with resultant minor distal weakness have been received as part of the continuing surveillance of PACLITAXEL FOR INJECTION safety. Optic nerve and/or visual disturbances (scintillating scotoma) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage. Postmarketing reports of ototoxicity (hearing loss and tinnitus) have been received.

Arthralgia/myalgia

There was no consistent relationship between dose or schedule of PACLITAXEL FOR INJECTION and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated in single-agent trials experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after PACLITAXEL FOR INJECTION administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Alopecia

Alopecia was observed in almost all patients.

Gastrointestinal

Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

In the first-line Phase III ovarian carcinoma study, the incidence of nausea and vomiting when PACLITAXEL FOR INJECTION was administered in combination with cisplatin appeared to be greater compared with the database for single-agent PACLITAXEL FOR INJECTION in ovarian and breast carcinoma. In the same study, diarrhea of any grade was reported more frequently (16%) compared to the control arm (8%) ($p=0.008$), but there was no difference for severe diarrhea.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of PACLITAXEL FOR INJECTION safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with PACLITAXEL FOR INJECTION alone and in combination with other chemotherapeutic agents.

In patients with poor-risk AIDS-related Kaposi's sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79% and 28% of patients, respectively. One third of patients with Kaposi's sarcoma complained of diarrhea prior to study start.

Hepatic

No relationship was observed between liver function abnormalities and either dose or schedule of PACLITAXEL FOR INJECTION administration. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. There is no evidence that PACLITAXEL FOR INJECTION when given as a 3-hour infusion to patients with mildly abnormal liver function causes exacerbation of abnormal liver function. Prolonged exposure to PACLITAXEL FOR INJECTION was not associated with cumulative hepatic toxicity.

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

Renal

Among the patients treated for Kaposi's sarcoma with PACLITAXEL FOR INJECTION, five patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other four patients had renal insufficiency with reversible elevations of serum creatinine.

Injection Site Reactions

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

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

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

Other

Transient skin changes due to PACLITAXEL FOR INJECTION-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with PACLITAXEL FOR INJECTION administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

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

Reports of asthenia and malaise have been received as part of the continuing surveillance of PACLITAXEL FOR INJECTION safety. In the Phase III trial of PACLITAXEL FOR INJECTION 135 mg/m² over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/ cisplatin.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known antidote for PACLITAXEL FOR INJECTION overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (see PRECAUTIONS, Pediatric Use section).

DOSAGE AND ADMINISTRATION

Note: Undiluted concentrate should not come in contact with plasticized PVC equipment. In order to minimize patients exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted PACLITAXEL FOR INJECTION solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

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

All patients should be premedicated prior to PACLITAXEL FOR INJECTION administration in order to reduce the risk of severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and 6 hours before PACLITAXEL FOR INJECTION, diphenhydramine 50 mg I.V. (or its equivalent), 30 to 60 minutes prior to PACLITAXEL FOR INJECTION, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before PACLITAXEL FOR INJECTION.

Metastatic carcinoma of the ovary

The administration of PACLITAXEL FOR INJECTION at a dose of 175 mg/m² over 3 hours in combination with cisplatin 75 mg/m² every 3 weeks is recommended for the primary treatment of patients with advanced carcinoma of the ovary. PACLITAXEL FOR INJECTION should be given before cisplatin when used in combination.

In patients previously treated with chemotherapy, the recommended regimen is 175 mg/m² administered intravenously over 3 hours every 3 weeks.

Carcinoma of the breast

For the adjuvant treatment of node-positive breast cancer, the recommended regimen is PACLITAXEL FOR INJECTION, at a dose of 175 mg/m² intravenously over 3 hours every 3 weeks for four courses administered sequentially to standard combination therapy.

After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, PACLITAXEL FOR INJECTION at a dose of 175 mg/m² administered intravenously over 3 hours every 3 weeks has been shown to be effective.

Non-small cell lung carcinoma

The recommended regimen, given every 3 weeks, is PACLITAXEL FOR INJECTION administered intravenously over 3 hours at a dose of 175 mg/m² followed by cisplatin.

Single courses of PACLITAXEL FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm³ and the platelet count is at least 100 000 cells/mm³. Patients who experience severe neutropenia (neutrophil < 500 cells/mm³) or severe peripheral neuropathy during PACLITAXEL FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLITAXEL FOR INJECTION.

AIDS-related Kaposi's Sarcoma

PACLITAXEL FOR INJECTION 135 mg/m² administered intravenously over 3 hours with a 3 week interval between courses or 100 mg/m² administered intravenously over 3 hours with a 2 week interval between courses (dose intensity 45-50 mg/m²/week). In the two clinical trials evaluating these schedules (see CLINICAL TRIALS: AIDS-Related Kaposi's Sarcoma), the former schedule (135 mg/m² every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m² every 2 weeks).

Based upon the immunosuppression observed in patients with advanced HIV disease, the following modifications are recommended in these patients.

- 1) the dose of dexamethasone as one of the three premedication drugs should be reduced to 10 mg orally.
- 2) treatment with PACLITAXEL FOR INJECTION should be initiated or repeated only if the neutrophil count is at least 1,000 cells/mm³.
- 3) the dose of subsequent courses of PACLITAXEL FOR INJECTION should be reduced by 20% for those patients who experience severe neutropenia (<500 cell/mm³ for a week or longer).
- 4) concomitant hematopoietic growth factor (G-CSF), should be initiated as clinically indicated.

Preparation and Administration Precautions

PACLITAXEL FOR INJECTION is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling PACLITAXEL FOR INJECTION. The use of gloves is recommended. Following topical exposure, tingling, burning, redness have been observed. If PACLITAXEL FOR INJECTION solution contacts the skin, wash the skin immediately and thoroughly with soap and water.

If PACLITAXEL FOR INJECTION contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea

have been reported. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see PRECAUTIONS and ADVERSE REACTIONS; Injection Site Reaction).

Preparation for Intravenous Administration

PACLITAXEL FOR INJECTION for Injection must be diluted prior to infusion. PACLITAXEL FOR INJECTION should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (15-25°C) and room lighting conditions; infusions should be completed within this timeframe. There have been rare reports of precipitation with longer than the recommended 3-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

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

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

Devices with spikes should not be used with vials of PACLITAXEL FOR INJECTION since they can cause the stopper to collapse resulting in loss of sterile integrity of PACLITAXEL FOR INJECTION solution.

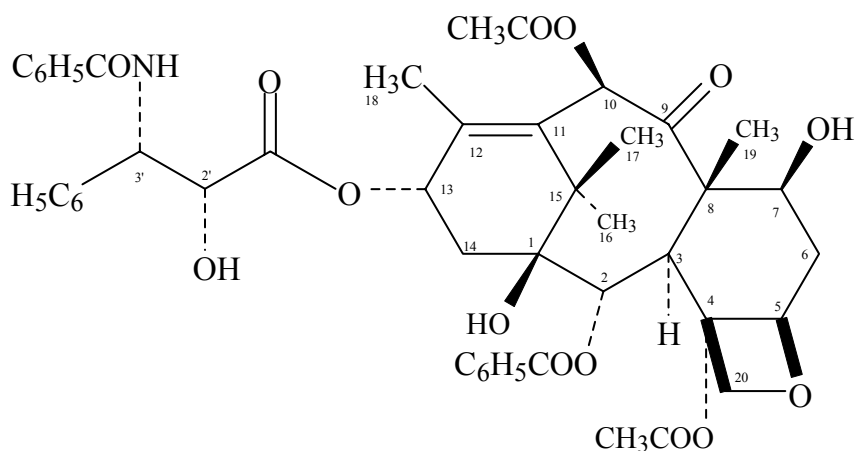
PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Proper Name: Paclitaxel

Chemical Name: Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,-12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2a*R*-[2a α ,4 β ,4a β ,6 β ,9 α (α *R**, β *S**),11 α ,12 α ,12a α ,12b α]]-; (2)(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,-12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

Structural Formula:



Molecular Formula: $C_{47}H_{51}NO_{14}$

Molecular Weight: 853.9

Description: Paclitaxel is a white to off-white crystalline powder. It is highly lipophilic and insoluble in water. It has a melting point of 216-223°C.

II. COMPOSITION

Each mL of PACLITAXEL FOR INJECTION contains 6 mg paclitaxel, 527 mg of polyoxyethylated castor oil, 2 mg citric acid and 49.7% (v/v) dehydrated alcohol, USP.

III. STABILITY AND STORAGE RECOMMENDATIONS

PACLITAXEL FOR INJECTION should be stored at room temperature (15-25°C). Retain in the original package and protect from light. Once punctured, the 5 and 25 mL vials of PACLITAXEL FOR INJECTION are stable for 28 days at room temperature protected from light.

Solutions for infusion prepared as recommended may be stored at room temperature (15-25°C) only if necessary. However, the infusion should be initiated within 24 hours of reconstitution.

If unopened vials are refrigerated, a precipitate may form which redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

IV. PREPARATION FOR INTRAVENOUS ADMINISTRATION

Contact of undiluted PACLITAXEL FOR INJECTION with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended (see DOSAGE AND ADMINISTRATION).

Prior to infusion, PACLITAXEL FOR INJECTION should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit.

PACLITAXEL FOR INJECTION should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

V. SPECIAL INSTRUCTIONS

1. Preparation of PACLITAXEL FOR INJECTION should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).
2. Personnel preparing PACLITAXEL FOR INJECTION should wear PVC gloves, safety glasses, disposable gowns and masks.
3. All needles, syringes, vials and other materials which have come in contact with PACLITAXEL FOR INJECTION should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.
4. Personnel regularly involved in the preparation and handling of PACLITAXEL FOR INJECTION should have bi-annual blood examinations.

AVAILABILITY OF DOSAGE FORMS

PACLITAXEL FOR INJECTION is available in multidose vials of 5 mL and 25 mL containing respectively 30 mg and 150 mg paclitaxel at a concentration of 6 mg/mL

PHARMACOLOGY

In vitro

PACLITAXEL FOR INJECTION exhibits cytotoxic activity against a wide variety of both human and rodent tumor cell lines *in vitro* including leukemia, non-small cell lung carcinoma, small cell lung carcinoma, colon carcinoma, CNS carcinoma, melanoma, renal carcinoma, ovarian carcinoma and breast carcinoma at IC₅₀ concentration (defined as the concentration required to inhibit cell proliferation to 50% of that of untreated control cells) in the nM range. PACLITAXEL FOR INJECTION blocks cell replication in the late G2 and/or M phases of the cell cycle. Additionally, PACLITAXEL FOR INJECTION produces unusual cytoskeletons characterized by discrete bundles or microtubules and the formation of abnormal spindle asters during mitosis. As a consequence of the disruption of the microtubule cytoskeleton, PACLITAXEL FOR INJECTION inhibits a variety of cell functions including chemotaxis, migration, cell spreading, polarization, generation of hydrogen peroxide and killing of phagocytosed microorganisms.

In addition to its ability to induce microtubule polymerization, exposure of murine macrophages to PACLITAXEL FOR INJECTION results in the release of tumor necrosis factor- α (TNF- α) accompanied by down regulation of the receptor.

In Vivo

PACLITAXEL FOR INJECTION has shown antitumor activity against many tumor models including leukemias and solid tumors and human solid xenografts. The table that follows summarizes PACLITAXEL FOR INJECTION's activity.

Tumor, Site	Form	Route	Activity
MURINE LEUKEMIAS			
L1210, ip	*	ip	Borderline → modest
P388, ip	*	ip	Mild
P1534, ip	*	ip	Mild → substantial
MURINE SOLID TUMORS			
ADJ/PC 6, ip	*	ip	Mild
C26, ip	*	ip	Mild
B16, ip	*	ip	Moderate → potentially curative
M109, ip	*	ip	Moderate → potentially curative
M109, ip (staged)	**	ip	Moderate → substantial
M109, sc	**	sc	Moderate
M109 src	**	sc	Moderate

Tumor, Site	Form	Route	Activity
HUMAN TUMOR XENOGRAFTS			
CX-1, src	*	sc	Mild → substantial
LOX, ip	*	ip	Moderate → potentially curative
MX-1, src	*	sc	Potentially curative
A431, src	**	iv	Substantial
A2780, src	**	iv	Substantial
A2780, sc	**	iv	Moderate
H2981, src	**	iv	Substantial
HCT-116	**	iv	Moderate
L2987, src	**	iv	Moderate
LX-1, src	**	iv	Moderate

* Suspension in hydroxypropylcellulose

** PACLITAXEL FOR INJECTION in ethanol/cremophor diluted with saline

Clinical trials

Ovarian Carcinoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
<p><i>First-Line data:</i> Phase 3 multicenter, randomized, controlled trial conducted by GOG, comparing therapy with PACLITAXEL FOR INJECTION (T) in combination with cisplatin (c) to cyclophosphamide (AC) in combination with cisplatin (c)</p>	<p>- 135 mg/m² of T over 24 hrs + 75 mg/m² of c - 750 mg/m² of AC + 75 mg/m² of c</p>	410	Stage III or IV disease (> 1 cm residual disease after staging laparotomy or distant metastases) with no prior chemotherapy	Patients treated with T in combination with cisplatin has 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.
<p><i>Second-Line data:</i> Phase 3 multicenter, bifactorial, randomized trial comparing two dosage regimens of PACLITAXEL FOR INJECTION (T) irrespective of the schedules and two schedules irrespective of dose.</p>	<p>- 175 mg/m² of T over 24 hrs - 175 mg/m² of T over 3 hrs - 135 mg/m² of T over 24 hrs - 135 mg/m² of T over 3 hrs</p>	407	Patients (pts) who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary.	<p>Pts receiving the 175 mg/m² dose had a response rate (RR) similar to that for those receiving the 135 mg/m² dose: 18% vs. 14% (p=0.28). No difference in RR was detected when comparing the 3-hr with the 24-hr infusion: 15% vs. 17% (p=0.50). Pts receiving the 175 mg/m² dose of T had a longer time to progression (TTP) than those receiving the 135 mg/m² dose: median 4.2 vs. 3.1 months (p=0.03). The median TTP for pts receiving the 3-hour vs. the 24-hr infusion were 4.0 months vs. 3.7 months, respectively. Median survival was 11.6 months in pts receiving the 175 mg/m² dose of T and 11.0 months in pts receiving the 135 mg/m² dose (p=0.92). Median survival was 11.7 months for pts receiving the 3-hr infusion of T and 11.2 months for pts receiving the 24-hr infusion (p=0.91).</p>

First-Line data: The adverse event profile for patients receiving PACLITAXEL FOR INJECTION in combination with cisplatin was consistent with that seen in previous clinical studies (see ADVERSE REACTIONS).

Second -Line data: In addition to the Phase 3 trial described above, data from five Phase 1 and 2 clinical studies 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 PACLITAXEL FOR INJECTION in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. PACLITAXEL FOR INJECTION 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 in previous clinical studies (see ADVERSE REACTIONS).

The results of this randomized study support the use of PACLITAXEL FOR 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.

Breast Carcinoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
<p><i>Adjuvant Breast Carcinoma Study:</i> Phase 3 multicenter, 3X2 factorial, randomized trial, conducted by CALGB, ECOG, NCCTG and SWOG, comparing adjuvant therapy with PACLITAXEL FOR INJECTION (T) to no further chemotherapy following four courses of doxorubicin (A) and cyclophosphamide (C)</p>	<p>600 mg/m² of C + A at doses of either</p> <ul style="list-style-type: none"> - 60 mg/m² (on day 1), - 75 mg/m² (in two divided doses on days 1 and 2), or - 90 mg/m² (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) <p>every 3 weeks for four courses and either</p> <ul style="list-style-type: none"> - 175 mg/m² of T over 3 hrs every 3 weeks for four additional courses or - no additional chemotherapy. <p>Patients (pts) whose tumors were +ve were to receive subsequent tamoxifen (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.</p>	3170	Node-positive breast carcinoma following either mastectomy or segmental mastectomy and nodal dissections.	<p>Median follow-up was 30.1 months. Of 2066 pts who were hormone receptor positive, 93% received tamoxifen. Based on a multivariate Cox model for disease-free survival, pts on AC+T had 22% risk reduction of disease recurrence compared to pts on AC (Hazard Ratio [HR] = 0.78, 95% CI 0.67-0.91, p = 0.0022) and 26% reduction in the risk of death (HR = 0.74, 95% CI 0.60-0.92, p = 0.0065). Increasing the dose of A higher than 60 mg/m² had no effect on either disease-free survival or overall survival. Subset analyses including number of positive lymph nodes, tumor size, hormone receptor status, and menopausal status showed a reduction in hazard similar to above for disease-free and overall survival in all larger subsets with one exception; pts with receptor-positive tumors had a smaller reduction in hazard (HR = 0.92) for disease-free survival with T than other groups.</p>

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
<i>After Failure of Initial Chemotherapy:</i> Phase 3 multicenter, randomized trial comparing two dosage regimens of PACLITAXEL FOR INJECTION (T).	- 175 mg/m ² of T over 3 hrs - 135 mg/m ² of T over 3 hrs	471	Patients (pts) who failed chemotherapy either in the adjuvant (30%) or metastatic (39%) setting or both (31%). At study entry, 60% had symptomatic disease with impaired performance status and 73% had visceral metastases.	The overall response rate was 26% (95% CI: 22 to 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4-18.1 + months). Overall, 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).

Adjuvant Breast Carcinoma Study: The adverse event profile for patients receiving PACLITAXEL FOR INJECTION subsequent to AC was consistent with that seen in previous clinical studies (see ADVERSE REACTIONS).

After Failure of Initial Chemotherapy: In addition to the Phase 3 trial described above, data from three Phase 2 clinical studies were used in support of the use of PACLITAXEL FOR INJECTION in patients with metastatic breast carcinoma. The adverse event profile for patients receiving PACLITAXEL FOR INJECTION subsequent to AC was consistent with that seen in previous clinical studies (see ADVERSE REACTIONS).

Non-Small Cell Lung Carcinoma (NSCLC)

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
Phase 3 multicenter, open label, randomized trial conducted by ECOG, comparing two dosage regimens of PACLITAXEL FOR INJECTION (T) in combination with cisplatin (c) to cisplatin (c) followed by etoposide (VP)	<p>- 135 mg/m² of T over 24 hrs + 75 mg/m² of c</p> <p>- 250 mg/m² of T over 24 hrs + 75 mg/m² of c with G-CSF support</p> <p>- 75 mg/m² of c on day 1 followed by 100 mg/m² of VP on days 1, 2 and 3 (control)</p>	599	Non-Small Cell Lung Cancer	There were statistically significant differences favoring each of the T plus c arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either T plus c arm and the c plus VP arm. In this 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 T at 135 mg/m ² of T as a 24-hr infusion + 75 mg/m ² of c. For all other factors, there was no difference in the treatment groups.

The adverse event profile for patients who received PACLITAXEL FOR INJECTION in combination with cisplatin was consistent with that seen in previous clinical studies (see ADVERSE REACTIONS).

AIDS-Related Kaposi's Sarcoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
CA139-174: Phase 2 single-centre, open-label, non-randomized study to assess the activity of PACLITAXEL FOR INJECTION (T) against AIDS-related Kaposi's Sarcoma.	135 mg/m ² of T over 3 hrs every 3 weeks (intended dose intensity 45 mg/m ² /wk). If no dose-limiting toxicity was observed, subjects were to receive 155 mg/m ² / and 175 mg/m ² in subsequent courses. Hematopoietic growth factors were not to be used initially.	29	AIDS-related Kaposi's sarcoma for which systemic chemotherapy was warranted	Objective response rate was 69%, including two complete responses (CR) and 18 partial responses (PR). An additional 28% of patients achieved stabilization of disease. Response rate for patients receiving prior systemic therapy was 79% (including 2 CRs and 13 Prs). Median time to response was 11.9 wks (range: 2.9 to 19.0 wks). Median duration of response was 7.0 months (range 3.5 to 29.2 months).
CA139-281: Phase 2, two-centre, open-label, non-randomized study to assess the efficacy and safety of PACLITAXEL FOR INJECTION (T) in patients with advanced AIDS-related Kaposi's Sarcoma.	100 mg/m ² of T over 3 hrs every 2 weeks (intended dose intensity 50 mg/m ² /wk). Patients could be receiving hematopoietic growth factors before the start of PACLITAXEL FOR INJECTION therapy or this support was to be initiated as indicated; the dose of PACLITAXEL FOR INJECTION was not increased.	56		Objective response rate was 59% (95% C.I.: 45% to 77%), including one complete response (CR) and 32 partial responses (PR). An additional 25% of patients achieved stabilization of disease. Response rate for patients receiving prior systemic therapy was 55% (22 PRs). Median time to response was 6.1 wks (range: 4.0 to 36.0 wks). Median duration of response was 10.4 months (range 2.8 to 18+ months).

All patients had widespread and poor-risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease (T1), 88% had a CD4 count <200 cells/mm³ (I1), and 97% had poor risk considering their systemic illness (S1).

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

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

Cutaneous Tumor Response (Amended ACTG Criteria): The objective response rate was 63% (95% CI: 49% to 75%) (37 of 59 patients) in patients with prior systemic therapy. Cutaneous responses were primarily defined as flattening of more than 50% of previously raised lesions.

The median time to response was 8.1 weeks and the median duration of response measured from the first day of treatment was 9.1 months (95% CI: 6.9 - 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 PACLITAXEL FOR INJECTION 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 (See ADVERSE REACTIONS). In this immunosuppressed patient population, however, a lower dose intensity of PACLITAXEL FOR INJECTION and supportive therapy including hematopoietic growth factors in patients with severe neutropenia are recommended. (See DOSAGE AND ADMINISTRATION). Patients with AIDS-related Kaposi's sarcoma may have more severe hematologic toxicities than patients with solid tumors. (See ADVERSE REACTIONS).

TOXICOLOGY

ACUTE TOXICITY

Species / Strain	No. / Sex / Group	Route	LD₅₀ (mg/kg)
Rat/Sprague-Dawley	5 M/F (RF) ^a 10 M/F (L) ^b	ip ip	34 (combined)
Rat/Sprague-Dawley	10 M/F	ip	M: 32 F: 36
Rat/Sprague-Dawley	5 M/F	iv	>85
Dog/Beagle	1 M/F	iv	>9

^a Range-Finding phase

^b Lethality phase

Signs of toxicity in rats were lethargy, rough coat, thinness, hunched posture, neck abscesses, soft stool, decreased body weight, squinted eyes, alopecia.

Signs of toxicity in dogs were decreased body weight.

SUBACUTE TOXICITY

Species/Strain	No./ Group	Sex	Dose Range ^a mg/kg/day	Route	Duration	Drug Related Findings
Mouse/CD2F ₁	5 5	M F	0, 1-15	iv	5 Days	No drug related toxicities.
Mouse/CD2F ₁	5 5	M F	0, 1-15*	ip	5 Days	<u>20 and 45 mg/kg/day</u> : Decreased body weight >10% <u>45 mg/kg/day</u> : Rough coat, thin/hunched posture. All died.
	15 15	M F	0, 21-43**	ip	5 Days	<u>≥24 mg/kg/day</u> : Dose-related decreased body weight, rough coat, thin/hunched posture, ataxia, hypothermia, squinted eyes and dyspnea, deaths (74/88 M, 56/90 F).
Rat/Sprague-Dawley	5 5	M F	0, 5-45*	ip	5 Days	<u>≥8.66 mg/kg/day</u> : Dose-related decreased body weight, rough coat, thin/hunched posture, stool changes, soiling, hypothermia, eye tearing and squinting, abscesses, deaths [(19/20 M, 18/20 F)*; (44/70 M at all doses, 26/40 F)**].
	10 10	M F	0, 5.3-14.2**	ip	5 Days	
Mouse/CD2F ₁	10 10	M F	Negative ^b Control	ip	5 Days	<u>1/2 LD₁₀, LD₁₀ and LD₅₀ dose groups</u> : Necrosis of developing spermatocytes. Giant cell formation.
	10 10	M F	Vehicle Control			<u>LD₁₀ and LD₅₀ dose groups</u> : Decrease in reticulocyte and neutrophil values. Lower liver and testicular weights. Moderate to severe thymic cortical lymphoid depletion. Necrosis or atrophy of small intestinal mucosa and crypt cell hypoplasia. Neurophilic hyperplasia, eosinopenia, lymphoid hypoplasia and atypical megakaryocytes, deaths (2/10 M, 8/10 F at LD ₁₀ ; 8/10 M, 9/9 F at LD ₅₀).
	10 10	M F	1/2 LD ₁₀ 10.79 13.05			
	10 10	M F	LD ₁₀ 21.57 26.09			<u>All dose groups</u> : Dose-related decreased body weight, lethargy, rapid respiration, rough coat, thin/hunched posture, hypothermia, squinted eyes with exudate.
	10 10	M F	LD ₅₀ 25.50 29.52			

SUBACUTE TOXICITY (cont'd)

Species/Strain	No./ Group	Sex	Dose Range ^a mg/kg/day	Route	Duration	Drug Related Findings
Rat/Sprague-Dawley	10	M	Negative ^b	ip	5 Days	<p><u>LD₅₀ dose group</u>: Testicular necrosis, visceral peritoneum inflammation (F only), deaths (3/10 M, 3/10 F).</p> <p><u>LD₁₀ and LD₅₀ dose groups</u>: Markedly decreased leukocyte and platelet counts. Weight loss, bone marrow hypoplasia, deaths (1/10 M, 3/10 F at LD₁₀).</p> <p><u>All dose groups</u>: Dose related thymic and splenic lymphoid depletion, rough coat, thin/hunched posture, lethargy, soft stool, neck abscesses. Decreased reticulocyte counts, white foci in submandibular lymph nodes and/or salivary glands.</p>
	10	F	control			
	10	M	Vehicle			
	10	F	Control			
	10	M	1/2 LD ₁₀			
	10	F	2.55 4.29			
10	M	LD ₁₀				
10	F	5.11 8.58				
10	M	LD ₅₀				
10	F	7.47 9.99				
Dog/Beagle	1 1	M F	0, 0.375, 0.75, 1.5, 3.0, 6.0	iv	5 Days	<p><u>All doses</u>: Decreased body weight. Increased ALT, cholesterol, triglycerides and total lipids. Intestinal hemorrhage or agonal changes. Lymphoid depletion of tonsils and/or bronchial lymph node.</p> <p><u>≥1.5 mg/kg/day</u>: Marked decreases in leukocyte, reticulocyte, platelet, and erythrocyte counts.</p> <p><u>≤1.5 mg/kg/day</u>: Moderate to severe bone marrow hematopoietic hypoplasia.</p> <p><u>3.0 to 6.0 mg/kg/day</u>: Deaths (All)</p>

* Range Finding phase

** Lethality phase

^a PACLITAXEL FOR INJECTION dissolved in Cremophor® EL (50%): ethanol (50%) and then diluted with saline to provide dosing solutions

^b Untreated

CHRONIC TOXICITY

Species/ Strain	No./ Group	Sex	Dose* (mg/kg/day)	Route	Duration	Drug Related Findings
Rat/Sprague-Dawley	10	M	Neg. Cont., saline	iv	1 Month	<p><u>3.3 mg/kg/day</u>: Slight decreases in erythrocyte, neutrophil and platelet counts and hemoglobin and hematocrit values; moderate decreases in leukocyte counts. Increased splenic extramedullary hematopoiesis and bone marrow hypoplasia. Moderate to severe decrease in reticulocyte counts. Minimal increase in lymphocyte counts.</p> <p><u>10 mg/kg/day</u>: Rough coat, alopecia, decreased body weight/weight gain and food and water intakes. Slight decreases in erythrocyte and neutrophil counts, hemoglobin and hemocrit values; moderate to severe decreases in reticulocyte count and slight increases in platelet and relative lymphocyte counts. Decreased weight of thymus, testes and seminal vesicles. Lower weights of testes and epididymides present at end of observation period.</p> <p>Microscopically, increased splenic extra medullary hematopoiesis and lymphoid depletion, thymic atrophy and lymphoid depletion, mandibular lymph node atrophy of lymph follicle, and lymphadenitis; bone marrow hypoplasia; hypospermatogenesis and atrophy of seminiferous tubules; glandular atrophy in seminal vesicle and prostate and giant cell formation in the epididymides.</p>
	10	F				
	10	M	Vehicle Control			
	10	F				
	10	M	1, 3.3, 10			
	10	F				
Dog/Beagle	5	M	Neg. Cont., saline	iv	1 Month	<p><u>0.3 and 1 mg/kg/day</u>: Reversible minimal decreases in bone marrow cellularity.</p> <p><u>3 mg/kg/day</u>: Interdigital cysts, swollen infusion sites, and transient decreased weight gain and food intake. Decreased erythrocyte numbers, hemoglobin concentration and hemocrit (M/F) and decreased leucocyte (severe neutropenia) counts in individual females. Lymphoid depletion of spleen or lymph nodes, duodenal inflammation and crypt dilation, decreased bone marrow cellularity, skin lesions and giant cell formation in the testes and epididymides. Residual drug-effects present in some lymphoid organs, duodenum, testes and skin at the end of recovery period.</p>
	5	F				
	3	M	Vehicle Control			
	3	F				
	3	M	0.3, 1			
	3	F				
	5	M	3			
	5	F				

* PACLITAXEL FOR INJECTION in Cremophor® EL: ethanol (50/50) diluted with saline for dosing solutions

REPRODUCTION AND TERATOLOGY

Species/ Strain	No./ Group	Sex	Route	Dose* and Frequency	Drug Related Findings
SEGMENT I Rat/Sprague- Dawley	20 20	M F	iv	0 (vehicle), 0 (saline) 0.1, 0.3, 1.0 mg/kg M: 63 days prior to mating and during mating F: During mating and through day 7 of gestation	Body weight gain and food intake were lower in F ₀ males and females Days 25-63 and Days 28-62, respectively, of pre-mating period. Body weight gain and food intake were lower in F ₀ females during Days 2-20 of gestation at the high dose level. Fertility indices in the F ₀ generation were lower at 1 mg/kg/day compared to saline and vehicle control groups. Copulation indices were similar to control.
	20	F		0 (Non-treated)	Adrenal, uterine and ovarian weights lower in F ₀ dams compared to controls. Numbers of corpora lutea, implantations and live fetuses were decreased, and numbers of empty implantation sites and fetal deaths were increased at 1 mg/kg/day. The no-effect dose was 0.3 mg/kg/day in both F ₀ and F ₁ generations.
SEGMENT II Rabbit/New Zealand White	20	F	iv	0 (saline), 0 (vehicle), 0.3, 1, 3 mg/kg, Days 6-18 of presumed gestation.	Twelve of 20 does given the high dose died or were sacrificed as moribund. Clinical signs of toxicity in the does that died included red excreta, stool consistency changes, decreased activity, food intake decreases and body weight loss. Liver and kidney weights were increased and ovary weights were decreased in the does given the high dose. Litter group mean values for corpora lutea, litter size, live fetuses and the number of does with viable fetuses in the high dose group were reduced. Litter group mean values for resorption (total or early), percentage of dead or resorbed conceptuses and the number of does with all conceptuses dead or resorbed were increased in the high dose group. In summary, PACLITAXEL FOR INJECTION at 3 mg/kg/day caused severe maternal toxicity (mortality, abortions, clinical signs and reduced organ weights, body weights and food consumption) and severe developmental toxicity (reduced corpora lutea, litter size and live fetuses and increased resorption). PACLITAXEL FOR INJECTION doses as high as 1 mg/kg/day did not cause any maternal or fetal toxicity.

* PACLITAXEL FOR INJECTION in Cremophor® EL: ethanol 50/50 diluted with saline for dosing solutions.

MUTAGENECITY AND GENOTOXICITY

PACLITAXEL FOR INJECTION was not mutagenic in the Ames/Salmonella and Escherichia Coli WP2 reverse mutation assays but was found to be clastogenic, in the *in vitro* cytogenetics assay in primary human lymphocytes.

PACLITAXEL FOR INJECTION was genotoxic *in vivo* on the mouse erythropoietic system in the mouse bone marrow erythrocyte micronucleus assay.

REFERENCES

1. Berg S.L., Cowan K.H., Balis F.M., et al
Pharmacokinetics of Taxol and doxorubicin administered alone and in combination by continuous 72-hour infusion
J Nat Can Inst 1994; 86:143-145
2. Brown T., Havlin K., Weiss G., Cagnola J., Kuhn J., Rizzo J., Craig J., Phillips J., and Van Hoff D.
A phase I trial of taxol given by a 6-hour intravenous infusion
J Clin Oncol 1991; 9: 1261-1267.
3. Cabral F.R., Wible L., Brenner S., and Brinkley B.R.
Taxol-requiring mutant of Chinese hamster ovary cells with impaired mitotic spindle assembly.
J Cell Biol 1983; 97: 30-39.
4. Capri G., Munzone E., Tarenzi E., et al
Optic nerve disturbances: A new form of paclitaxel neurotoxicity
J Nat Cancer Inst. 1994; 86: 1099-1101
5. DeBrabander M.
A model for the microtubule organizing activity of the centrosomes and kinetochores in mammalian cells
Cell Biol Int Rep 1982; 6: 901-915.
6. Donehower R.C., Rowinsky E.K., Grochow L.B., et al.
Phase I trial of taxol in patients with advanced cancer
Cancer Treat Reports 1987; 71(12): 1171-1177.
7. Dorr R.T., Snead K., Liddil, J.D.
Skin Ulceration Potential of Paclitaxel in a Mouse Skin Model *In Vivo*
Cancer 1996; 78(1): 152-156.
8. Einzig A.I., Wiernik P.H., and Schwartz E.L.
Taxol: A new agent active in melanoma and ovarian cancer
In New Drugs, Concepts and Results in Cancer Chemotherapy, FM Muggia (ed.), pp. 89-100. Kluwer Academic Publishers, Inc. (1992).
9. Gianni L., Kearns C.M., Giani A., et al
Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans
J Clin Oncol 1995; 13: 180-190
10. Grem T.L., Tutsch K.D., Simon K.J., Alberti D.B., Willson J.K.V., Tormey D.C., Swaminathan S., Trump D.L.
Phase I study of taxol administered as a short iv infusion daily for 5 days
Cancer Treat Reports 1987; 71(12): 1179-1184.

11. Harris J.W., Rahman A., Kim B.-R., et al
Metabolism of TAXOL by human hepatic microsomes and liver slices: Participation of cytochrome P450 3A4 and an unknown P450 enzyme
Cancer Res 1994; 54: 4026-4035
12. Kecker R.W., Jamis-Dow C.A., Egorin M.J., et al
Effect of cimetidine, probenecid, and ketoconazole on the distribution, biliary secretion, and metabolism of [³H] TAXOL in the Sprague-Dawley rat
Drug Metab Disposit 1994; 22: 254-258
13. Legha S.S., Tenney D.M., Krakoff I.R.
Phase I study of taxol using a 5-day intermittent schedule
J Clin Oncol 1986; 4(5): 762-766.
14. Manfredi J.J. and Horwitz S.B.
An antimetabolic agent with a new mechanism of action
Pharmacol Ther 1984; 25: 83-125.
15. Manfredi J.J., Parness J., and Horwitz S.B.
Taxol binds to cellular microtubules
J Cell Biol 1982; 94: 688-696.
16. McGuire W.P., Rowinsky E.K., Rosenshein N.B., Grumbine F.C., Ettinger D.S., Armstrong D.K., and Donehower R.C.
Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms
Ann Int Med 1989; 111: 273-279.
17. McGuire W.P., Hoskins W.J., Brady M.F., Kugera P.R., Partridge E.E., Look K.Y., Clarke-Pearson D.L. and Davidson M.
Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer
New Eng J Med 1996; 334: 1-6.
18. Mole-Bajer J. and Bajer A.S.
Action of taxol on mitosis: modification of microtubule arrangements and function of the mitotic spindle in Haemanthus endosperm
J Cell Biol 1983; 96: 527-540.
19. O'Shaghnessy J.A., Fisherman J.S., Cowan K.H.
Combination paclitaxel (TAXOL) and doxorubicin therapy for metastatic breast cancer
Sem Oncol 1994; 21(suppl 8): 19-23
20. Roberts L.P., Nath J., Friedman M.M. and Gallin J.I.
Effects of taxol on human neutrophils
J Immunol 1982; 129: 2134-2141.
21. Rowinsky E.K., Burke P.J., Karp J.E., Tucker R.W. Ettinger D.S., and Donehower R.C.
Phase I and pharmacodynamic study of taxol in refractory acute leukemias
Cancer res 1989 49: 4640-4647.
22. Rowinsky E.K., Cazenave L.A., and Donehower R.C.

- Taxol: a novel investigational antimicrotubule agent
J Natl Canc Inst 1990; 82: 1247-1259.
23. Rowinsky E.K., Gilbert M.R., McGuire W.P., Noe D.A., Grochow L.B., Forastiere A.A., Erringer D.S., Lubejko B.G. Clark B., Sartorius S.E., Cornblath D.R., Hendricks C.B. and Donehower R.C.
Sequences of taxol and cisplatin: A Phase I and pharmacologic study
J Clin Oncol 1991; 9(9): 1692-1703.
 24. Sarosy G., Kohn E., Stone D.A., Rothenberg M., Jacob J., Adamo D.O., Ognibene F.P., Cunnoin R.E. and Reed E.
Phase I study of taxol and granulocyte colony-stimulating factor in patients with refractory ovarian cancer
J Clin Oncol 1992; 10(7): 1165-1170
 25. Schiff P.B. and Horwitz S.B.
Taxol stabilizes microtubules in mouse fibroblast cells
Proc Natl Acad Sci, USA 1980; 77: 1561-1565.
 26. Seidman A.D., Barrett S., Canezo S.
Photopsia during 3-hour paclitaxel administration at doses ≥ 250 mg/m²
J Clin Oncol 1994; 12: 1741-1742
 27. Slichenmyer W.J., and Von Hoff D.D.
Taxol: A new and effective anti-cancer drug
Anti-Cancer Drugs 1991; 2: 519-530.
 28. Turner P.F. and Margolis R.L.
Taxol-induced bundling of brain-derived microtubules
J Cell Biol 1984; 99: 940-946.
 29. Venook A.P., Egorin M., Brown T.D., et al
Paclitaxel (Taxol) in patients with liver dysfunction (CALGB 9264)
pROC asco 1994; 13: 139 (Abstract #350)
 30. Waugh W.N., Trissel L.A., and Stella V.J.
Stability, compatibility and plasticizer extraction of taxol injection diluted in infusion solutions and stored in various containers
Am J Hosp Pharm 1991; 48: 1520-1524.
 31. Weiss R.B., Donehower R.C., Wiernik P.H. et al.
Hypersensitivity reactions from taxol
J Clin Oncol 1990; 8: 1263-1268.
 32. Wiernik P.H., Schwartz E.L., Strauman J.J., Dutcher J.P., Lipton R.B., and Einzig A.
Phase I trial of taxol given as a 24-hour infusion every 21 days: Responses observed in metastatic melanoma
J Clin Oncol 1987; 5(8): 1232-1239.

33. Wiernik P.H., Schwartz E.L., Strauman J.J., Dutcher J.P., Lipton R.B., and Paietta E. Phase I clinical and pharmacokinetic study of taxol
Cancer Res 1987; 47: 2486-2493.
34. Wright M., Monsarrat B., Alvinerie P., et al
Hepatic metabolism and biliary excretion of taxol. Second National Cancer Institute Workshop on Taxol and Toxus. Alexandria, Virginia (1992)
35. Kelly K., Crowley J., Bunn P.A., et al
A Randomized Phase III Trial of Paclitaxel Plus Carboplatin (PC) Versus Vinorelbine Plus Cisplatin (VC) in Untreated Advanced Non-Small Cell Lung Cancer (NSCLC): A Southwest Oncology Group (SWOG) Trial
36. Norton L., Slamon D., Leyland-Jones B., et al
Overall Survival (OS) Advantage to Simultaneous Chemotherapy (Crx) Plus the Humanized Anti-HER2 Monoclonal Antibody Herceptin (H) in HER2-Overexpressing (HER2+) Metastatic Breast Cancer (MBC)
37. Walsky RL., Obach RS., Gaman EA., et al
Selective inhibition of human cytochrome P450 2C8 by montelukast.
Drug Metab Dispos 2005; Mar 33(3):413-8.
38. Walsky RL., Gaman EA., Obach RS.
Examination of 209 drugs for inhibition of cytochrome P450 2C8
J Clin Pharmacol 2005; Jan 45(1):68-78.