PRODUCT MONOGRAPH

[Pr] PACLITAXEL FOR INJECTION

(paclitaxel)
Injection, 6 mg/mL

Teva Standard

Antineoplastic Agent

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Toronto, Ontario
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(paclitaxel)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Injection	6 mg/mL	Ethanol, Cremophor (macrogolglycerol ricinoleate) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PACLITAXEL FOR INJECTION (PACLITAXEL) 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 H_2 ANTAGONISTS (SUCH AS DEXAMETHASONE, DIPHENHYDRAMINE AND CIMETIDINE OR RANITIDINE) TO MINIMIZE HYPERSENSITIVITY REACTIONS (SEE DOSAGE AND ADMINISTRATION). SEVERE HYPERSENSITIVITY REACTIONS CHARACTERIZED BY DYSPNEA AND HYPOTENSION REQUIRING TREATMENT, ANGIOEDEMA, AND GENERALIZED URTICARIA HAVE OCCURRED IN PATIENTS RECEIVING PACLITAXEL. 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.

PACLITAXEL FOR INJECTION (paclitaxel) is indicated, alone or in combination, for the treatment of carcinoma of the:

- Ovary

- Breast
- Lung
- 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 DETAILED 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.

Geriatrics:
No data is available.

Pediatrics:
The safety and effectiveness of paclitaxel in pediatric patients have not been established (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

CONTRAINDICATIONS

- PACLITAXEL FOR INJECTION (paclitaxel) is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (macrogolglycerol ricinoleate). For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- PACLITAXEL FOR INJECTION should not be used in patients with severe baseline neutropenia (<1,500 cells/mm^3) nor in patients with AIDS-related Kaposi's Sarcoma with baseline or subsequent neutrophil counts of <1,000 cells/mm^3.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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 H_2 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. 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).

General

PACLITAXEL FOR INJECTION should be administered as a diluted infusion.

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) or plastic bags (polyolefin) and administered through non-PVC administration sets.

Hypersensitivity Reactions

Patients with a history of severe hypersensitivity reactions to products containing Cremophor† EL should not be treated with PACLITAXEL FOR INJECTION (see 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.

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at 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 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. Page 6

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.

Cardiovascular

Severe cardiac conduction abnormalities have been reported in < 1% of patients during paclitaxel 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).

Hypotension, hypertension and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. In severe cases, paclitaxel 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 ADVERSE REACTIONS).

Hematologic

PACLITAXEL FOR INJECTION should not be administered to patients with baseline

neutrophil counts of less than 1,500 cells/mm^3 (see 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/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (< 500 cells/mm^3) 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/mm^3. (See DOSAGE AND ADMINISTRATION).

Hepatic

There is evidence that the toxicity of paclitaxel 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).

Neurologic

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).

Special Populations

Pregnant Women: PACLITAXEL FOR INJECTION may cause fetal harm when administered to a pregnant woman. Paclitaxel 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 Women: It is not known whether paclitaxel is excreted in human milk. Breast feeding should be discontinued for the duration of PACLITAXEL FOR INJECTION therapy.

Pediatrics: The safety and effectiveness of paclitaxel 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 was infused intravenously

over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel 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 use in this population.

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).

Geriatrics: No data is available.

Monitoring and Laboratory Tests

PACLITAXEL FOR INJECTION should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (<1,000 cells/mm^3 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/mm^3 (>1,000 cells/mm^3 for patients with Kaposi's Sarcoma) and platelets recover to a level >100,000 cells/mm^3 (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The frequency and severity of adverse events are generally similar between patients receiving paclitaxel 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 at doses ranging from 135-300 mg/m^2/day and schedules of 3 or 24 hours. Data from a subset of 181 patients treated at the recommended dose of 175 mg/m^2 and a 3-hour infusion schedule is also included in the table.

		135-300 mg/m^2 % of Patients N=812	**175 mg/m^2 % of Patients N=181**
Bone Marrow			
Neutropenia	< 2,000/mm3	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
Hypersensitivity Reactions			
All		41	40
Severe		2	1
Cardiovascular			
Bradycardia (first 3 hours of infusion)		3	3
Hypotension (first 3 hours of infusion)		12	11
Severe events		1	2
Abnormal ECG			
All Patients		23	13
Patients with normal baseline		14	8
Peripheral Neuropathy			
Any symptoms		60	64
Severe symptoms		3	4
Myalgia/Arthralgia			
Any symptoms		60	54
Severe symptoms		8	12
Gastrointestinal			
Nausea and vomiting		52	44
Diarrhea		38	25
Mucositis		31	20
Alopecia		87	93

	135-300 mg/m^2 % of Patients N=812	175 mg/m^2 % of Patients N=181
Hepatic (Patients with normal baseline)		
Bilirubin elevations	7	4
Alkaline phosphatase elevations	22	18
AST elevations	19	18
Injection site reactions	13	4

Safety referring to a large randomized trial of paclitaxel (135 mg/m^2 over 24 hours) / cisplatin (75 mg/m^2) versus cyclophosphamide/cisplatin, including 410 patients (196 receiving paclitaxel), has been evaluated. The combination of paclitaxel 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 subsequent to cyclophosphamide and doxorubicin was consistent with that seen in the pooled analysis of data from 812 patients treated with single-agent paclitaxel in 10 clinical studies.

SUMMARY OF 3-HOUR INFUSION DATA AT A DOSE OF 175 mg/m^2

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/m^2 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 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. Compared to 24-hour infusion schedules, neutropenia was less common when paclitaxel 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 KAPOSI'S SARCOMA

The following table shows the frequency of important adverse events in the 85 patients with Kaposi's Sarcoma (KS) treated with two different single-agent paclitaxel 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)
Bone Marrow			
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
Opportunistic Infections			
Any		76	54
Cytomegalovirus		45	27
Herpes Simplex		38	11
Pneumocystis carinii		14	21
M. avium intracellulare		24	4
Candidiasis, esophageal		7	9
Cryptosporidiosis		7	7
Cryptococcal meningitis		3	2
Leukoencephalopathy		—	2
Hypersensitivity Reaction[c]			
All		14	9
Cardiovascular			
Hypotension		17	9
Bradycardia		3	—
Peripheral Neuropathy			
Any		79	46
Severe**		14	16
Myalgia/Arthralgia			
Any		93	48
Severe**		14	16

	Percent of Patients	
	Study CA139-174 135/3[b]/3 wk (n = 29)	Study CA139-281 100/3[b]/2 wk (n = 56)
Gastrointestinal		
Nausea and vomiting	69	70
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 dose in mg/m^2/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 at a dose of 135 mg/m^2 every 3 weeks than in the study utilizing paclitaxel at a dose of 100 mg/m^2 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 DETAILED PHARMACOLOGY: 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 in 10 clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received paclitaxel in combination with cisplatin or in patients with breast cancer who received paclitaxel after doxorubicin/cyclophosphamide in the adjuvant setting, 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. 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 was bone marrow suppression. Neutropenia was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (<500 cells/mm^3) occurred in 27% of patients treated at a dose of 175 mg/m^2, 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 was administered to patients with ovarian carcinoma at a dose of 175 mg/m^2/3 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 plus cisplatin arm and in the control arm.

When paclitaxel 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 135 mg/m^2/24 hours plus cisplatin) and 65% (paclitaxel 250 mg/m^2/24 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 175 mg/m^2/3 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/m^2 and 26% of the patients given 175 mg/m^2 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/mm^3 at least once while on treatment; 7% had a platelet count < 50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these

events was unrelated to the paclitaxel dose and schedule. In the Phase 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 (see WARNINGS AND PRECAUTIONS section). The frequency and severity of HSR were not affected by the dose or schedule of paclitaxel 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 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 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 occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at

175 mg/m^2 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 135 mg/m^2/24 hours plus cisplatin), 12% (paclitaxel 250 mg/m^2/24 hours plus cisplatin and G-CSF), and 6% (paclitaxel 175 mg/m^2/3 hours plus cisplatin) when paclitaxel followed by cisplatin was administered to patients with advanced NSCLC; there was a similar incidence in the non-paclitaxel 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. Page 12

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 safety.

Respiratory: Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism, have been received as part of the continuing surveillance of paclitaxel 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. 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 discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of

paclitaxel 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 therapy. In the Intergroup first-line ovarian carcinoma study, the regimen with paclitaxel 175 mg/m^2 by 3-hour infusion followed by cisplatin 75 mg/m^2 resulted in greater incidence and severity of neurotoxicity (reported as neuromotor or neurosensory events) than the regimen containing cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2 , 87% (21% severe) versus 52% (2% severe), respectively. In the GOG first-line ovarian carcinoma study, the regimen with paclitaxel (135 mg/m^2 over 24 hours) followed by cisplatin (75 mg/m^2) resulted in an incidence of neurotoxicity (reported as peripheral neuropathy) that was similar to the regimen containing cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2, 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in Intergroup and GOG trials suggests that when paclitaxel is given in combinations with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m^2 given by 3-hour infusion (21%) than at a dose of 135 mg/m^2 given by 24-hour infusion (3%). In patients with NSCLC, administration of paclitaxel 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. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving paclitaxel 135 mg/m^2 by 24-hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide.

Other than peripheral neuropathy, serious neurologic events following paclitaxel 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 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.

Arthralgia/myalgia: There was no consistent relationship between dose or schedule of paclitaxel 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 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 was administered in combination with cisplatin appeared to be greater compared with the database for single-agent paclitaxel 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 safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel 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 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 when given as a 3-hour infusion to patients with mildly abnormal liver function causes exacerbation of abnormal liver function. Prolonged exposure to paclitaxel 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 safety.

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

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 safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety. In the Phase III trial of paclitaxel 135 mg/m^2 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.

Post-Market Adverse Drug Reactions

Postmarketing reports of ototoxicity (hearing loss and tinnitus) have been received.

DRUG INTERACTIONS

Overview

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with known

substrates, inducers or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-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, 17α-ethinyl estradiol, retinoic acid, montelukast and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

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

Drug-Drug Interactions

Cisplatin
In a Phase I trial in which paclitaxel was administered as a 24-hour infusion and cisplatin was administered as a 1 mg/min infusion, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e. paclitaxel before cisplatin). When paclitaxel is given before cisplatin, the safety profile of paclitaxel 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 was administered following cisplatin. Therefore, paclitaxel 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.

Doxorubicin
Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered BEFORE doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin administered over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and 3-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Drug interactions are summarised in the following table.

Established or Potential Drug-Drug Interactions

Paclitaxel	Ref	Effect	Clinical comment
Cisplatin	CT	A decrease in paclitaxel clearance when paclitaxel was administered following cisplatin.	Paclitaxel should be given before cisplatin when used in combination.
Doxorubicin	CT	Plasma levels of doxorubicin and its active metabolite may be increased when paclitaxel and doxorubicin are used in combination.	Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered BEFORE doxorubicin and using longer than recommended infusion times.

Legend: CT = Clinical Trial

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
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) or plastic bag (polyolefin) and administered through non-PVC administration sets.

PACLITAXEL FOR INJECTION should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use filter devices which incorporate non-PVC fluid pathways.

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.

Recommended Dose and Dosage Adjustment

Metastatic carcinoma of the ovary
The administration of PACLITAXEL FOR INJECTION at a dose of 175 mg/m^2 over 3 hours in combination with cisplatin 75 mg/m^2 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/m^2 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/m^2 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 at a dose of 175 mg/m^2 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/m^2 followed by cisplatin.

Single courses of PACLITAXEL FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100 000 cells/mm^3. Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3) 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 135 mg/m^2 administered intravenously over 3 hours with a 3 week interval between courses or 100 mg/m^2 administered intravenously over 3 hours with a 2 week interval between courses (dose intensity 45-50 mg/m^2/week). In the two clinical trials evaluating these schedules (see CLINICAL TRIALS: AIDS-Related Kaposi's Sarcoma), the former schedule (135 mg/m^2 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/m^2 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/mm^3.
3) the dose of subsequent courses of PACLITAXEL FOR INJECTION should be reduced by 20% for those patients who experience severe neutropenia (<500 cell/mm^3 for a week or longer).
4) concomitant hematopoietic growth factor (G-CSF), should be initiated as clinically indicated.

Missed Dose
In the event that a dose is missed the opinion of an oncologist should be sought.

Administration
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).

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.

Preparation for Intravenous Administration

PACLITAXEL 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 (15-30^{o}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.

Admixtures of PACLITAXEL FOR INJECTION should be used within 24 hours. Unused portions should be discarded.

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 or polyolefin containers. Non-PVC containing administration sets 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.

OVERDOSAGE

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage 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).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

In vitro, paclitaxel 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).

Pharmacokinetics

Absorption: The pharmacokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m^2, and infusion schedules ranging from 3 to 24 hours. Following intravenous administration of paclitaxel, 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/m^2 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/m^2.

Variability in systemic paclitaxel exposure, as measured by $AUC_{0-\infty}$ 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.

Distribution: The disposition of paclitaxel has not been fully elucidated in humans. Mean steady state volume of distribution has ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

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.

Metabolism: *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 WARNINGS AND PRECAUTIONS: Drug Interactions). The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Excretion: Following 3 hour infusions of 175 mg/m^2, mean terminal half-life was estimated to be 9.9 hours; mean total body clearance was 12.4 L/h/m^2.

After intravenous administration of paclitaxel, 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/m^2 dose of radiolabeled paclitaxel 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.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of paclitaxel in the pediatric population have not been established.

Geriatrics: The pharmacokinetics of paclitaxel in the geriatric population have not been established.

Gender: The pharmacokinetics of paclitaxel based on gender differences have not been established.

Race: The pharmacokinetics of paclitaxel based on race differences have not been established.

Hepatic Insufficiency: The effect of hepatic insufficiency on the disposition of paclitaxel has not been investigated.

Renal Insufficiency: The effect of renal insufficiency on the disposition of paclitaxel has not been investigated.

Genetic Polymorphism: The pharmacokinetics of paclitaxel based on genetic polymorphism differences have not been established.

STORAGE AND STABILITY

PACLITAXEL FOR INJECTION should be stored at room temperature (15-30^{o}C). Retain in the original package and protect from light. Once punctured, the 5 and 16.7 mL vials of PACLITAXEL FOR INJECTION are stable for 28 days at room temperature. The 50 mL pharmacy bulk vial should be used within 24 hours after initial entry.

Solutions for infusion prepared as recommended may be stored at room temperature (15-30^{o}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.

SPECIAL HANDLING 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^{o}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.

5. Directions for Dispensing from Pharmacy Bulk Vial
The use of Pharmacy Bulk Vial is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. Dispensing from the Pharmacy Bulk Vial should be completed within 24 hours after initial entry.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PACLITAXEL FOR INJECTION is available in multidose vials of 5 mL and 16.7 mL and pharmacy bulk vial of 50 mL containing respectively 30 mg, 100 mg and 300 mg paclitaxel at a concentration of 6 mg/mL.

Each mL of PACLITAXEL FOR INJECTION contains paclitaxel 6 mg, macrogolglycerol ricinoleate (Cremophor) 527 mg, dehydrated ethanol 49.7% v/v and anhydrous citric acid 2 mg.

PACLITAXEL FOR INJECTION is latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

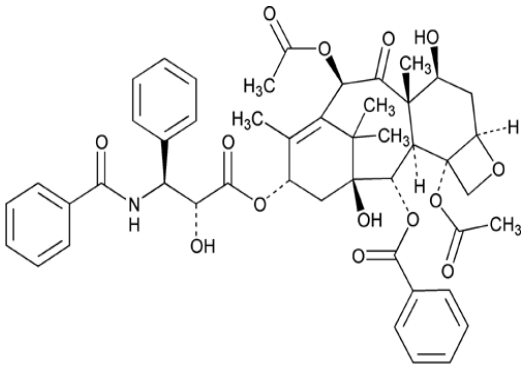
Common name: Paclitaxel

Chemical name: Benzenepropanoic acid, β-(benzoyloamino)-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-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl ester, [2aR-2aα,4β,4aβ,6β,9α (αR*,βS*), 11α, 12α, 12aα, 12bα]]

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

Molecular mass: 853.92

Structural formula:



Physicochemical properties: Paclitaxel is a white powder with a melting point of 209.3 - 216.7°C. It is soluble in methanol, ethanol, chloroform, ethyl acetate and dimethylsulfoxide, insoluble in water. Solubility in water is less than 0.5 mg/mL.

DETAILED PHARMACOLOGY

In vitro

Paclitaxel 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 IC_{50} concentration (defined as the concentration required to inhibit cell proliferation to 50% of that of untreated control cells) in the nM range. Paclitaxel blocks cell replication in the late G2 and/or M phases of the cell cycle. Additionally, paclitaxel 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 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 results in the release of tumor necrosis factor-α (TNF-α) accompanied by down regulation of the receptor.

In Vivo

Paclitaxel has shown antitumor activity against many tumor models including leukemias and solid tumors and human solid xenografts. The table that follows summarizes paclitaxel'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
HUMAN TUMOR XENOGRAFTS			

Tumor, Site	Form	Route	Activity
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 in ethanol/cremophor diluted with saline

CLINICAL TRIALS
Ovarian Carcinoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
First-Line data: Phase 3 multicenter, randomized, controlled trial conducted by GOG, comparing therapy with paclitaxel (P) in combination with cisplatin (c) to cyclophosphamide (AC) in combination with cisplatin (c)	- 135 mg/m^2 of P over 24 hrs + 75 mg/m^2 of c - 750 mg/m^2 of AC + 75 mg/m^2 of c	410	Stage III or IV disease (> 1 cm residual disease after staging laparotomy or distant metastases) with no prior chemotherapy	Patients treated with P 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.
Second-Line data: Phase 3 multicenter, bifactorial, randomized trial comparing two dosage regimens of paclitaxel (P) irrespective of the schedules and two schedules irrespective of dose.	- 175 mg/m^2 of P over 24 hrs - 175 mg/m^2 of P over 3 hrs - 135 mg/m^2 of P over 24 hrs - 135 mg/m^2 of P over 3 hrs	407	Patients (pts) who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary.	Pts receiving the 175 mg/m^2 dose had a response rate (RR) similar to that for those receiving the 135 mg/m^2 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/m^2 dose of P had a longer time to progression (TTP) than those receiving the 135 mg/m^2 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/m^2 dose of P and 11.0 months in pts receiving the 135 mg/m^2 dose (p=0.92). Median survival was 11.7 months for pts receiving the 3-hr infusion of P and 11.2 months for pts receiving the 24-hr infusion (p=0.91).

First-Line data: The adverse event profile for patients receiving paclitaxel 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 in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Paclitaxel 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 at doses of 135 to 175 mg/m^2 , 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
Adjuvant Breast Carcinoma Study: Phase 3 multicenter, 3x2 factorial, randomized trial, conducted by CALGB, ECOG, NCCTG and SWOG, comparing adjuvant therapy with paclitaxel (P) to no further chemotherapy following four courses of doxorubicin (A) and cyclophosphamide (C)	600 mg/m^2 of C + A at doses of either - 60 mg/m^2 (on day 1), - 75 mg/m^2 (in two divided doses on days 1 and 2), or - 90 mg/m^2 (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for four courses and either - 175 mg/m^2 of P over 3 hrs every 3 weeks for four additional courses or - no additional chemotherapy. 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.	3170	Node-positive breast carcinoma following either mastectomy or segmental mastectomy and nodal dissections.	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+P 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/m^2 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 P than other groups.

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
After Failure of Initial Chemotherapy: Phase 3 multicenter, randomized trial comparing two dosage regimens of paclitaxel (P).	- 175 mg/m^2 of P over 3 hrs - 135 mg/m^2 of P 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% Cl: 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 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 in patients with metastatic breast carcinoma. The adverse event profile for patients receiving paclitaxel 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 (P) in combination with cisplatin (c) to cisplatin (c) followed by etoposide (VP)	- 135 mg/m^2 of P over 24 hrs + 75 mg/m^2 of c - 250 mg/m^2 of P over 24 hrs + 75 mg/m^2 of c with G-CSF support - 75 mg/m^2 of c on day 1 followed by 100 mg/m^2 of VP on days 1, 2 and 3 (control)	599	Non-Small Cell Lung Cancer	There were statistically significant differences favoring each of the P plus c arms for response rate and time to tumor progression. There was no statistically significant difference in survival between either P 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 P at 135 mg/m^2 of P 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 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 (P) against AIDS-related Kaposi's Sarcoma.	135 mg/m^2 of P 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 (P) in patients with advanced AIDS-related Kaposi's Sarcoma.	100 mg/m^2 of P 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 therapy or this support was to be initiated as indicated; the dose of paclitaxel 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/mm^3 (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/m^2 /week in Study CA139-174 and 50 mg/m^2 /week in Study CA139-281), delivered dose intensity was 38-39 mg/m^2 /week in both studies, with a similar range (20-24 to 51-61).

Efficacy: The efficacy of paclitaxel 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 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 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	LD_{50} (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	20 and 45 mg/kg/day: Decreased body weight >10% 45 mg/kg/day: Rough coat, thin/hunched posture. All died.
	15 15	M F	0, 21-43**	ip	5 Days	≥24 mg/kg/day: 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	≥8.66 mg/kg/day: 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	

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Mouse/CD2F$_1$	10 10	M F	Negative[b] Control	ip	5 Days	1/2 LD_{10}, LD_{10} and LD_{50} dose groups: Necrosis of developing spermatocytes. Giant cell formation.
	10 10	M F	Vehicle Control			LD_{10} and LD_{50} dose groups: 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			All dose groups: Dose-related decreased body weight, lethargy, rapid respiration, rough coat, thin/hunched posture, hypothermia, squinted eyes with exudate.
	10 10	M F	LD_{10} 21.57 26.09			
	10 10	M F	LD_{50} 25.50 29.52			

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Rat/Sprague-Dawley	10	M	Negative[b] control	ip	5 Days	$\underline{LD_{50}\text{ dose group}}$: Testicular necrosis, visceral peritoneum inflammation (F only), deaths (3/10 M, 3/10 F).
	10	F				
	10	M	Vehicle Control			$\underline{LD_{10}\text{ and }LD_{50}\text{ dose groups}}$: Markedly decreased leukocyte and platelet counts. Weight loss, bone marrow hypoplasia, deaths (1/10 M, 3/10 F at LD_{10}).
	10	F				
			1/2 LD_{10}			$\underline{\text{All dose groups}}$: Dose related thymic and splenic lymphoid depletion, rough coat, thin/hunched posture, lethargy, soft stool, neck abscesses. Decreased reticulocycte counts, white foci in submandibular lymph nodes and/or salivary glands.
	10	M	2.55			
	10	F	4.29			
			LD_{10}			
	10	M	5.11			
	10	F	8.58			
			LD_{50}			
	10	M	7.47			
	10	F	9.99			

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Dog/Beagle	1 1	M F	0, 0.375, 0.75, 1.5, 3.0, 6.0	iv	5 Days	All doses: Decreased body weight. Increased ALT, cholesterol, triglycerides and total lipids. Intestinal hemorrhage or agonal changes. Lymphoid depletion of tonsils and/or bronchial lymph node. ≥1.5 mg/kg/day: Marked decreases in leukocyte, reticulocyte, platelet, and erythrocyte counts. ≤1.5 mg/kg/day: Moderate to severe bone marrow hematopoietic hypoplasia. 3.0 to 6.0 mg/kg/day: Deaths (All)

* Range Finding phase

** Lethality phase

[a] Paclitaxel 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 10 10 10 10 10	M F M F M F	Neg. Cont., saline Vehicle Control 1, 3.3, 10	iv	1 Month	3.3 mg/kg/day: 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. 10 mg/kg/day: 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. Microspopically, 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.
Dog/Beagle	5 5 3 3 3 3 5 5	M F M F M F M F	Neg. Cont., saline Vehicle Control 0.3, 1 3	iv	1 Month	0.3 and 1 mg/kg/day: Reversible minimal decreases in bone marrow cellularity. 3 mg/kg/day: 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.

* Paclitaxel 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 20	M F 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 0 (Non-treated)	Body weight gain and food intake were lower in F_0 males and females Days 25-63 and Days 28-62, respectively, of premating 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. 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 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 doses as high as 1 mg/kg/day did not cause any maternal or fetal toxicity.

* Paclitaxel in Cremophor† EL: ethanol 50/50 diluted with saline for dosing solutions.

MUTAGENECITY AND GENOTOXICITY

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

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PART III: CONSUMER INFORMATION

PrPACLITAXEL FOR INJECTION
Paclitaxel

This leaflet is part III of a three-part "Product Monograph" published when PACLITAXEL FOR INJECTION was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PACLITAXEL FOR INJECTION. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PACLITAXEL FOR INJECTION is a prescription cancer medicine. It is injected into a vein and it is used to treat different types of tumors. The tumors include advanced ovary and breast cancer. The tumors also include certain lung cancers (non-small cell) in people who cannot have surgery or radiation therapy. PACLITAXEL FOR INJECTION may also be used to treat AIDS-related Kaposi's sarcoma.

What it does:
Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

PACLITAXEL FOR INJECTION is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. PACLITAXEL FOR INJECTION may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by PACLITAXEL FOR INJECTION causing some of the side effects. (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM, below.)

When it should not be used:
Patients who have a history of hypersensitivity (allergic reactions) to PACLITAXEL FOR INJECTION or other drugs containing Cremophor® EL* (macrogolglycerol ricinoleate), like cyclosporine or teniposide, should not be given PACLITAXEL FOR INJECTION.

In addition, PACLITAXEL FOR INJECTION should not be given to patients with dangerously low white blood cell counts.

What the medicinal ingredient is:
Paclitaxel

What the nonmedicinal ingredients are:
Each mL of PACLITAXEL FOR INJECTION contains paclitaxel 6 mg, macrogolglycerol ricinoleate (Cremophor) 527 mg, dehydrated ethanol 49.7% v/v and anhydrous citric acid 2 mg.

What dosage forms it comes in:
PACLITAXEL FOR INJECTION is available in multidose vials of 5 mL and 16.7 mL and pharmacy bulk vial of 50 mL containing respectively 30 mg, 100 mg and 300 mg paclitaxel at a concentration of 6 mg/mL.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **PACLITAXEL FOR INJECTION should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.**
- **Patients receiving paclitaxel injection should be pretreated with corticosteroids, antihistamines, and H_2 antagonists to reduce the chances of allergic reactions.**
- **Severe allergic reactions characterized by difficulty with breathing and low blood pressure requiring treatment, swelling, and generalized itching and hives have occurred in patients receiving paclitaxel.**
- **Rare fatal reactions have occurred in patients despite pre-treatment.**
- **Patients who experience severe hypersensitivity reactions to PACLITAXEL FOR INJECTION should not use the drug again.**

BEFORE you use PACLITAXEL FOR INJECTION talk to your doctor or pharmacist if:

- you are pregnant, become pregnant or plan to become pregnant while taking PACLITAXEL FOR INJECTION. PACLITAXEL FOR INJECTION could harm the unborn child when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with PACLITAXEL FOR INJECTION.

you are nursing a baby while taking PACLITAXEL FOR INJECTION. Studies have shown PACLITAXEL FOR

INJECTION to be present in the breast milk of animals receiving the drug, it may be present in human breast milk as well. Therefore, nursing a baby while taking PACLITAXEL FOR INJECTION is NOT recommended.

The safety and effectiveness of paclitaxel in paediatric patients have not been established. PACLITAXEL FOR INJECTION contains dehydrated alcohol; 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.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PACLITAXEL FOR INJECTION including:
Cisplatin
Doxorubicin

If you are taking any other medication on prescription or over the counter, let your doctor know before start of the therapy. Drug interactions with foods, herbal products, homeopathic preparations, and laboratory tests have not been established.

PROPER USE OF THIS MEDICATION

Usual dose:
The dose you are given depends on how big you are. It varies with your body surface area. Technically this is measured in square metres (m^2), but actually is worked out from your height and weight.

PACLITAXEL FOR INJECTION is injected into a vein [intravenous (I.V.) infusion]. Before you are given PACLITAXEL FOR INJECTION, you will have to take certain medicines (premedications) to prevent or reduce the chance you will have a serious allergic reaction. Such reactions have occurred in a small number of patients while receiving PACLITAXEL FOR INJECTION and have been rarely fatal. Your doctor will tell you about complete information on pretreatment with other drugs. (See SIDE EFFECTS AND WHAT TO DO ABOUT THEM, below)

Overdose:
In the case of an overdose your doctor will stop the therapy and treat the symptoms.

Missed Dose:
Your doctor will set the times at which you are to receive this medicine. If you think you may have missed a dose, contact your doctor as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most patients taking PACLITAXEL FOR INJECTION experience side effects, although it is not always possible to tell whether such effects are caused by PACLITAXEL FOR INJECTION another medicine they may be taking, or the cancer itself.

Allergic reactions. Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during PACLITAXEL FOR INJECTION infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash. The likelihood of a serious allergic reaction is lowered by the use of several kinds of medicines that are given to you before the PACLITAXEL FOR INJECTION (paclitaxel) Injection infusion.

Heart and blood vessel (cardiovascular) effects. PACLITAXEL FOR INJECTION may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. Your heart function, including blood pressure and pulse, will be monitored while you are receiving the medicine. You should notify your doctor if you have a history of heart disease.

Infections due to low white blood cell count. Among the body's defenses against bacterial infections are white blood cells. Between your PACLITAXEL FOR INJECTION treatment cycles, you will often have blood tests to check your white blood cell counts. PACLITAXEL FOR INJECTION usually causes a brief drop in white blood cells. If you have a fever (temperature above 38°C) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.

Hair loss. Complete hair loss, or alopecia, almost always occurs with PACLITAXEL FOR INJECTION. This usually involves the loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. Hair generally grows back after you've finished your PACLITAXEL FOR INJECTION treatment.

Joint and muscle pain. You may get joint and muscle pain a few days after your PACLITAXEL FOR INJECTION treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

Irritation at the injection site. PACLITAXEL FOR INJECTION sometimes causes irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling,

inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the I.V. (intravenous) fluid leaking into the surrounding area. If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.

Low red blood cell count. Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following PACLITAXEL FOR INJECTION treatment causing anemia. Some patients may need a blood transfusion to treat the anemia. Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following PACLITAXEL FOR INJECTION treatment.

Mouth or lip sores (mucositis). Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the PACLITAXEL FOR INJECTION treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

Numbness, tingling, or burning in the hands and/or feet (neuropathy). These symptoms occur often with PACLITAXEL FOR INJECTION and usually get better or go away without medication within several months of completing treatment. However, if you are uncomfortable, tell your doctor so that he/she can decide the best approach for relief of your symptoms.

Stomach upset and diarrhea. Some patients experience nausea, vomiting, and/or diarrhea following PACLITAXEL FOR INJECTION use. If you experience nausea or stomach upset, tell your doctor. Diarrhea will usually disappear without treatment; however, if you experience **severe** abdominal or stomach area pain and/or **severe** diarrhea, tell your doctor right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Stomach upset, nausea, vomiting, and/or diarrhea		✓	
	Low red blood cell count, anemia, feel tired, tire easily, appear pale, and become short of breath.		✓	
	Numbness, tingling, or burning in the hands and/or feet (neuropathy).	✓		
	Irritation at the injection site. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores).		✓	✓
	Joint and muscle pain.	✓		
	Hair loss. Complete hair loss, or alopecia, loss of eyebrows, eyelashes, and pubic hair, as well as scalp hair.	✓		
	Heart and blood vessel (cardiovascular) effects, drop in heart rate (bradycardia) and low blood pressure (hypotension).	✓		
	Allergic reactions. trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash.		✓	✓

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects

This is not a complete list of side effects. For any unexpected effects while taking PACLITAXEL FOR INJECTION, *contact your doctor or pharmacist.*

HOW TO STORE IT

Store all drugs properly and keep them out of the reach of children.

The expiry date is printed on the label. Do not use after this date.

PACLITAXEL FOR INJECTION should be stored at room temperature (15-30^{o}C). Retain in the original package and protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited at: 1-800-268-4127 ext. 5005
or druginfo@tevacanada.com

This leaflet was prepared by:
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