PRODUCT MONOGRAPH

[Pr] PACLitaxel INJECTION, USP

(paclitaxel)
Injection, 6 mg/mL

Antineoplastic Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 4
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 8
DRUG INTERACTIONS 18
DOSAGE AND ADMINISTRATION 20
OVERDOSAGE 24
ACTION AND CLINICAL PHARMACOLOGY 24
SPECIAL HANDLING INSTRUCTIONS 26
DOSAGE FORMS, COMPOSITION AND PACKAGING 27

PART II: SCIENTIFIC INFORMATION 28
PHARMACEUTICAL INFORMATION 28
DETAILED PHARMACOLOGY 34
TOXICOLOGY 35
REFERENCES 44

PART III: CONSUMER INFORMATION 48

[Pr] PACLitaxel INJECTION, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Solution for Injection, 6 mg/mL	Anhydrous citric acid, polyoxyl 35 castor oil, dehydrated alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PACLitaxel Injection, USP (paclitaxel) is indicated, alone or in combination, for:

- Treatment of carcinoma of the ovary, breast, or 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 **SCIENTIFIC INFORMATION** - Clinical Trials).
- Second-line treatment of metastatic carcinoma of the breast after failure of standard therapy.

Lung Carcinoma

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

Kaposi's Sarcoma

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

CONTRAINDICATIONS

- Patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyethoxylated castor oil).
- 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

- Should only be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents (see **INDICATIONS AND CLINICAL USE**).
- Paclitaxel for Injection should be administered as diluted infusion.
- Patients should be pre-treated with corticosteroids, antihistamines, and H_2 antagonist (see **Sensitivity/Resistance** section below).
- Should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm3 (see **Hematologic** section below).

General

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

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

Carcinogenesis and Mutagenesis

See section **TOXICOLOGY** under **SCIENTIFIC INFORMATION**.
Second Primary Malignancies: Acute myeloid leukemia and myelodysplatic syndrome have been reported in post-market reports.

Cardiovascular

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 infusion, is recommended. Continuous cardiac monitoring is not required except for patients who develop serious conduction abnormalities (see **ADVERSE REACTIONS**).

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 INJECTION, USP**.

Driving/Operating Machinery
Since **PACLITAXEL INJECTION, USP** contains ethanol (absolute alcohol), consideration should be given to the possibility of CNS and other effects.

Gastrointestinal
Severe mucositis has been reported which requires dose reduction (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION)**.

Pseudomembranous colitis has been reported in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhea occurring during or shortly after treatment with paclitaxel (see **ADVERSE REACTIONS)**.

Endocrine and Metabolism
Tumor lysis syndrome has been reported in post-market reports.

Hematologic
PACLITAXEL INJECTION, USP should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (see **CONTRAINDICATIONS**). 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. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving **PACLITAXEL INJECTION, USP**. Patients should not be re-treated with subsequent cycles of **PACLITAXEL INJECTION, USP** 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 INJECTION, USP** 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 INJECTION, USP**, 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/Biliary/Pancreatic
There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering **PACLITAXEL INJECTION, USP** to patients with moderate to severe hepatic impairment and dose adjustments should be considered (see **ADVERSE REACTIONS**).

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of pain, 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 three-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.

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 INJECTION, USP** for severe neuropathy (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION**).

When a combination of cisplatin and paclitaxel regimens is used as first-line treatment in women with advanced ovarian cancer, it has been reported that a three hour infusion of paclitaxel in combination with cisplatin may result in a greater incidence of severe neurotoxicity than paclitaxel followed by cisplatin. Paclitaxel when it is given in combination with a platinum compound, e.g. cisplatin, should be given before the platinum compound.

Paclitaxel for Injection contains ethanol (absolute alcohol), 396 mg/mL; consideration should be given to possible CNS and other effects of ethanol (absolute alcohol). Children may be more sensitive than the adults to the effects of ethanol (absolute alcohol); see **Special Populations** - Pediatrics.

Ophthalmologic

There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with Paclitaxel as well as with other taxanes (see **Post-Market Adverse Drug Reactions**). Most reports of CME have resolved after cessation of the taxane treatment. Patients with visual impairment during Paclitaxel treatment should seek a prompt and complete ophthalmologic examination. Paclitaxel should be discontinued if a CME diagnosis is confirmed.

Sensitivity/Resistance

Paclitaxel for Injection should be administered as a diluted infusion. Patients receiving Paclitaxel for Injection should be pre-treated 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 for Injection. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pre-treatment. In case of a severe hypersensitivity reaction, paclitaxel infusion should be discontinued immediately and the patient should not be rechallenged with the drug (see ADVERSE REACTIONS).

Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL should not be treated with **PACLITAXEL INJECTION, USP** (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 INJECTION, USP** and aggressive symptomatic therapy.

Sexual Health

Fertility: Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Special Populations

Pregnant Women: PACLITAXEL INJECTION, USP 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 INJECTION, USP**. If **PACLITAXEL INJECTION, USP** 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 INJECTION, USP** 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 three 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.

Geriatrics: No data is available.

Monitoring and Laboratory Tests

PACLITAXEL INJECTION, USP 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 INJECTION, USP** treatment. Patients should not be retreated with subsequent cycles of **PACLITAXEL INJECTION, USP** 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

Adverse Drug Reaction Overview

The frequency and severity of adverse events are generally similar between patients receiving paclitaxel for the treatment of ovarian, breast or non-small cell lung carcinoma. The most frequent significant undesirable effect of paclitaxel was bone marrow suppression. Neutropenia was dose and schedule dependent and was generally rapidly reversible.

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. Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm3 at least once while on treatment. 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.

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 and 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.

Hypotension, during the first three hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients.

Sixty percent of all patients treated in single-agent trials experienced arthralgia/myalgia; 8% experienced severe symptoms. Alopecia was observed in almost all patients. Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphate and AST (SGOT), respectively.

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 three or 24 hours. Data from a subset of 181 patients treated at the recommended dose of 175 mg/m^2 and a three-hour infusion schedule is also included in the table.

Table 1 - Incidences of adverse reactions from clinical trials in carcinoma of the ovary and of the breast involving patients treated with single-agent paclitaxel at doses ranging from 135-300 mg/m2/day and schedules of three or 24 hours.

		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	2
Cardiovascular			
Bradycardia (first three hours of infusion)		3	3
Hypotension (first three hours of infusion)		12	11
Severe events		1	2

	135-300 mg/m² % of Patients N=812	175 mg/m² % of Patients N=181
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
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/m² over 24 hours) / cisplatin (75 mg/m²) 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 Three-hour Infusion Data at a Dose of 175 mg/m²

Unless otherwise stated, the following safety data relate to 62 patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m² and a three-hour infusion schedule, in Phase III clinical trials. All patients were pre-medicated 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 three-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 for Injection. However, patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. Toxicities that were observed only in or were noted to have occurred with greater severity in the population with Kaposi's sarcoma and that occurred with a difference that was clinically significant in this population are described.

Hematologic

The most frequent significant undesirable effect of paclitaxel 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 seven 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 III 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 three-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 three-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 pre-medication prior to paclitaxel (see **WARNINGS AND PRECAUTIONS**). 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 three-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 three 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.

Cardiovascular

Hypotension, during the first three hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first three 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.

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 **DRUG INTERACTIONS**)

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 two 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 for Injection discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. In the Intergroup first-line ovarian carcinoma study, the regimen with paclitaxel 175 mg/m^2 by three-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 three-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.

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 three-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.

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 three-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.

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 pain, 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 three-hour infusion.

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.

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.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)
Cardiovascular: Cases of myocardial infarction have been reported rarely.
Gastrointestinal: Rare reports of neutropenic enterocolitis (typhlitis), despite the co-administration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.
Injection Site Reactions: 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.
Neurologic: Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (< 1%) and have included grand mal seizures, ataxia and encephalopathy.
Respiratory: Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Post-Market Adverse Drug Reactions
Carcinogenesis and Mutagenesis, Second Primary Malignancies: Acute myeloid leukemia and myelodysplastic syndrome have been reported.
Cardiovascular: Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety. Cardiomyopathy has been reported in very rare cases.
Endocrine and Metabolism: Tumor lysis syndrome has been reported.
Gastrointestinal: Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety.
General disorders and administration site conditions: Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.
Hepatic: Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.
Hypersensitivity Reactions (HSR): 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.

Infection and infestations: Pseudomembranous colitis has been reported.
Injection Site Reactions: 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.
Musculoskeletal and connective tissue: Systemic lupus erythematosus and scleroderma have been reported.
Neurologic: 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. Post-marketing reports of ototoxicity (hearing loss and tinnitus) have been received.
Ophthalmologic: There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with paclitaxel as well as with other taxanes (see **WARNINGS AND PRECAUTIONS**). Based on a number of literature cases, an association between CME and Paclitaxel is considered to be reasonably well established. Features specific to this clinical entity include an absence of vascular leakage with no other precipitating factors, and positive dechallenge in most cases.
Respiratory, thoracic and mediastinal disorders: Rare cases of respiratory failure, interstitial pneumonia, pulmonary embolism and lung fibrosis have been reported as post-marketing adverse drug reactions.
Skin and subcutaneous tissue disorders: Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and dermatitis exfoliative have been received as part of the continuing surveillance of paclitaxel safety.

DRUG INTERACTIONS

Serious Drug Interactions

- Should be given before cisplatin when used in combination (see **Drug-Drug Interactions**).
- Caution should be exercised when administering concomitantly with known substrates, inducers or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see **Drug-Drug Interactions**).

Overview

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 for Injection should be given before cisplatin when used in combination.

Cimetidine
The effect of cimetidine pre-medication on the metabolism of paclitaxel has been investigated; the clearance of paclitaxel was not affected by cimetidine pre-treatment.

Substrates, Inducers, Inhibitors of Cytochrome P450 2C8 and 3A4
The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering **PACLITAXEL INJECTION, USP** 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, vincristine, deferasirox, trimethoprim, and St. John's wort), 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 INJECTION, USP**.

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 for Injection and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and three-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

<u>Drug-Drug Interactions</u>
The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Paclitaxel	Ref	Effect	Clinical comment
Cisplatin	CT	↓ Paclitaxel clearance when paclitaxel was administered following cisplatin. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.	Paclitaxel for Injection should be given before cisplatin when used in combination.
Cimetidine	CT	No effect	The clearance of paclitaxel was not affected by cimetidine pre-treatment.
Ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, vincristinm, testosterone, 17 α-ethinyl estradiol, retinoic acid, montelukast, quercetin, deferasiroxand trimethoprim.	T	Metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited	Caution should be exercised when administering Paclitaxel for Injection concomitantly with known substrates, inducers or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.
Doxorubicin	T	More profound neutropenic and stomatitis episodes	Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when Paclitaxel for Injection and doxorubicin are used in combination.

Legend: C = Case Study, CT = Clinical Trial; T = Theoretical

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

Drug-Herb Interactions
Established or potential interactions with herbal products include St-John's Wort.

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Patients who experience severe neutropenia (neutrophil count <0.5 x 10^9/L for a minimum of 7 days) or severe peripheral neuropathy or severe mucositis should receive a dose reduced by 20%

(see **WARNINGS AND PRECAUTIONS**).

Metastatic carcinoma of the ovary

The administration of **PACLITAXEL INJECTION, USP** at a dose of 175 mg/m^2 over three 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 INJECTION, USP** 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 three hours every three weeks.

Carcinoma of the breast

For the adjuvant treatment of node-positive breast cancer, the recommended regimen is **PACLITAXEL INJECTION, USP**, at a dose of 175 mg/m^2 intravenously over three hours every three 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 three hours every three weeks has been shown to be effective.

Non-small cell lung carcinoma

The recommended regimen, given every three weeks, is **PACLITAXEL INJECTION, USP** administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin.

Single courses of **PACLITAXEL INJECTION, USP** 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 INJECTION, USP** therapy should have the dosage reduced by 20% for subsequent courses of **PACLITAXEL INJECTION, USP**.

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 INJECTION, USP** 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 INJECTION, USP** 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

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

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

All patients should be pre-medicated prior to Paclitaxel for Injection administration in order to reduce the risk of severe hypersensitivity reactions. Such pre-medication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and six hours before Paclitaxel for Injection, diphenhydramine 50 mg IV (or its equivalent), 30 to 60 minutes prior to Paclitaxel for Injection, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel for Injection.

Preparation 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 **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS).**

Reconstitution:

Parenteral Products:

Amount of finished product (6 mg/mL)	Common Diluents	Amount of diluent [1] (Theoretical fill)	Packaging system	Final Concentrations
5 mL	0.9% Sodium Chloride Injection Or 5% Dextrose Injection	100 mL	Non-PVC infusion bags (ie. Polyolefin bag) Or Glass Bottles	0.3 mg/mL
20 mL				1.2 mg/mL

Prior to the addition of drug, calculate the appropriate volume of diluent to be removed from packaging system to take into account the overage of diluent volume in the packaging system and the amount of drug to be added.

PACLITAXEL INJECTION, USP must be diluted prior to infusion. **PACLITAXEL INJECTION, USP** 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°C) and room lighting conditions; infusions should be completed within this time frame. There have been rare reports of precipitation with longer than the recommended three-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant loss in potency has been noted following simulated delivery of the solution through IV 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 INJECTION, USP** solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined should be used.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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 **WARNINGS AND PRECAUTIONS**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PACLITAXEL INJECTION, USP (paclitaxel) is an antimicrotubule antineoplastic agent. It promotes microtubule assembly by enhancing the polymerisation of tubulin, the protein subunit of spindle microtubules, even in the absence of the mediators normally required for microtubule assembly (e.g.guanosine triphosphate [GTP], thereby inducing the formation of stable, non-functional microtubules. While the precise mechanism of action of the drug is not completely known, paclitaxel disrupts the dynamic equilibrium within the microtubule system and blocks cells in the late G2 phase and M phase of the cell cycle, inhibiting cell replication and impairing function of nervous tissue.

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 **DETAILED PHARMOCOLOGY**).

Pharmacokinetics

Table 3 – Summary of paclitaxel's pharmacokinetic parameters in patients given doses of 135 and 175 mg/m^2 as three hour and 24 hours infusions.

	$t_{1/2}$ (h)	Clearance	Volume of distribution
Single dose mean	3.0 to 52.7 hours	11.6 to 24.0 L/h/m^2	198 to 688 L/m^2

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 three 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 three 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. Mean steady state volume of

distribution has ranged from 198 to 688 L/m^2 indicating extensive extravascular distribution and/or tissue binding.

Following three 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.

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: *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 mcg/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 **DRUG INTERACTIONS**). The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Excretion: The disposition of paclitaxel has not been fully elucidated in humans. 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 three-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.

STORAGE AND STABILITY

PACLITAXEL INJECTION, USP should be stored at room temperature (15-30^{o}C). Retain in the original package and protect from light. Once punctured, the 5 mL and 16.7 mL vials of **PACLITAXEL INJECTION, USP** are stable for up to 28 days at room temperature. The 50 mL pharmacy bulk vial should be used within 24 hours after initial entry. The solutions (admixture) are physically and chemically stable for up to 27 hours at ambient temperature (15-

30°) and room lighting conditions; infusions should be completed within this time frame.

Solutions for infusion prepared as recommended may be stored at room temperature (15-30°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.

As with all parenteral drug products, injections/intravenous ad-mixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

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 of **PACLITAXEL INJECTION, USP** should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

Personnel preparing **PACLITAXEL INJECTION, USP** should wear PVC gloves, safety glasses, disposable gowns and masks.

All needles, syringes, vials and other materials which have come in contact with **PACLITAXEL INJECTION, USP** should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

Personnel regularly involved in the preparation and handling of **PACLITAXEL INJECTION, USP** should have bi-annual blood examinations.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PACLITAXEL INJECTION, USP 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. The flip-off cap for the 5 mL and 50 mL fills is light yellow, and the flip-off cap for the 16.7 mL fill is light blue.

Each mL of **PACLITAXEL INJECTION, USP** contains paclitaxel 6 mg, Anhydrous Citric Acid 2 mg, Polyoxyl 35 Castor Oil 527 mg and Dehydrated Alcohol 49.7 % v/v.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

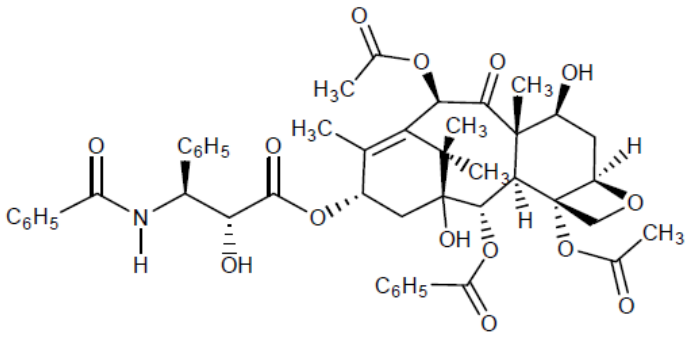
Common name: Paclitaxel

Chemical name: (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-1,2a, 3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclodeca[3,4]benz[1,2-b]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2R,3S)-N-benzoyl-3-phenylisoserine

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

Molecular Weight: 854

Structural Formula:



Description: Paclitaxel is a white to off-white crystalline powder with a melting point of 213.5-223°C. It is highly lipophilic and insoluble in water.

CLINICAL TRIALS

Clinical Trials

Ovarian Carcinoma

Study Design	Treatment / Doses	No. of Pts.	Population	Endpoints / Conclusion
First-Line data: Phase III 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 of 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 III 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 chemo-therapy 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-hr 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 III trial described above, data from five Phase I and II 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 six months from completion of, a platinum containing regimen) with response rates of 14% in the Phase III study and 31 % in the Phase I and II clinical studies. The adverse event profile in this Phase III 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 three-hour intravenous infusion. The same doses administered by 24-hour infusion were more toxic.

Breast Carcinoma

Study Design	Treatments / Doses	No. of Pts	Population	Endpoints / Conclusion
Adjuvant Breast Carcinoma Study: Phase III 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 cyclophospha-mide (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	3170	Node-positive breast carcinoma following either mastectomy or segmental mastec-tomy 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 analysis 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 Pts	Population	Endpoints / Conclusion
	mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.			

Breast Carcinoma (continued)

Study Design	Treatments / Doses	No. of Pts.	Population	Endpoints / Conclusion
After Failure of Initial Chemotherapy: Phase III 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% CI: 22 to 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4- 18.1 + months). Overall, the median time to progression was 3.5 months (range: 0.03- 17.1 months). Median survival was 11.7 months (range: 0- 18.9 months)

Adjuvant Breast Carcinoma Study: The adverse event profile for patients receiving paclitaxel 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 III trial described above, data from three Phase II 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 Pts.	Population	Endpoints / Conclusion
Phase III multicenter, open label, randomized trial conducted by ECOG, comparing two dosage regimens of paclitaxel (P) in combination with cisplatin [c] to	- 135 mg/m2 of P over 24 hrs + 75 mg/m2 of c - 250 mg/m2 of P over 24 hrs + 75 mg/m2 of c with G-CSF support	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

cisplatin [c] followed by etoposide (VP)	- 75 mg/m2 of c on day 1 followed by 100 mg/m2 of VP on days 1, 2 and 3 (control)			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).

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
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).

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-a (TNF-a) 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			

Tumor, Site	Form	Route	Activity
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			
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

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 15 15	M F M F	0, 1-15* 0, 21-43**	ip ip	5 days 5 days	20 and 45 mg/kg/day: Decreased body weight >10% 45 mg/kg/day: Rough coat, thin/hunched posture. All died. ≥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 10 10	M F M F	0, 5-45* 0, 5.3-14.2**	ip ip	5 days 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)**].

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Mouse/$CD2F_1$	1.0e + 19	M F M F M F M F M F	Negative[b] Control Vehicle Control 1/2 LD_{10} 10.79 13.05 LD_{10} 21.57 26.09 LD_{50} 25.50 29.52	ip	5 days	<u>1/2 LD_{10}, LD_{10} and LD_{50} dose groups</u>: Necrosis of developing spermatocytes. Giant cell formation. <u>LD_{10} and LD_{50} dose groups</u>: Decrease in reticulocyte and neutrophil values. Lower liver and testicular weights. Moderate to severe thymic cortical lymphoid depletion. Necrosis or atrophy of small intestinal mucosa and crypt cell hypoplasia. Neurophilic hyperplasia, eosinopenia, lymphoid hypoplasia and atypical megakaryocytes, deaths (2/10 M, 8/10 F at LD_{10}; 8/10 M, 9/9 F at LD_{50}). <u>All dose groups</u>: Dose-related decreased body weight, lethargy, rapid respiration, rough coat, thin/hunched posture, hypothermia, squinted eyes with exudate.

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Rat/Sprague-Dawley	1.0e + 19	M F M F M F M F M F	Negative[b] control Vehicle Control 1/2 LD_{10} 2.55 4.29 LD_{10} 5.11 8.58 LD_{50} 7.47 9.99	ip	5 days	LD_{50} dose group: Testicular necrosis, visceral peritoneum inflammation (F only), deaths (3/10 M, 3/10 F). LD_{10} and LD_{50} dose groups: Markedly decreased leukocyte and platelet counts. Weight loss, bone marrow hypoplasia, deaths (1/10 M, 3/10 F at LD_{10}). 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.
Dog/Beagle	11	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	1.01e+11	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 saline 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	M F	iv	0 (vehicle), 0 (saline) 0.1, 0.3, 1.0 mg/kg M: 63 days prior to mating and during mating F: During mating and through day 7 of gestation	Body weight gain and food intake were lower in F_0 males and females Days 25-63 and Days 28-62, respectively, of 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.
	20	F		0 (Non-treated)	Adrenal, uterine and ovarian weights lower in F_0 dams compared to controls. Numbers of corpora lutea, implantations and live fetuses were decreased, and numbers of empty implantation sites and fetal deaths were increased at 1 mg/kg/day. The no-effect dose was 0.3 mg/kg/day in both F_0 and F_1 generations.

Species/Strain	No./ Group	Sex	Route	Dose* and Frequency	Drug Related Findings
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

[Pr] PACLitaxel INJECTION, USP
Paclitaxel

This leaflet is part III of a three-part "Product Monograph" published when **PACLITAXEL INJECTION, USP** 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 INJECTION, USP**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for?
This medicine is used to treat:
- Ovarian cancer
- Breast cancer
- Lung cancer
- AIDS-related Kaposi's Sarcoma

What it does?
This medicine belongs to a group of medicines called antineoplastic or cytotoxic medicines. You may also hear of these being called chemotherapy medicines.

It works by killing cancer cells and stopping cancer cells from growing and multiplying.

When it should not be used?
If you have an allergy to:
- any medicine containing paclitaxel
- any of the ingredients listed at the end of this leaflet
- any medicines containing PEG 35 castor oil (Cremophor® EL), such as cyclosporin injection or teniposide injection.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

You must not be given this medicine if you have a very low white blood cell (WBC) count.

Tell your doctor if you have an infection or high temperature. Your doctor may decide to delay your treatment until the infection has gone. A mild illness, such as a cold, is not usually a reason to delay treatment.

If you are pregnant or plan to become pregnant.

What the medicinal ingredient is?
Paclitaxel

What the important nonmedicinal ingredients are?
Anhydrous citric acid, polyoxyl 35 castor oil, dehydrated alcohol.

What dosage forms it comes in?
PACLITAXEL INJECTION, USP 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
- **Should only be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.**
- **Patients should be pre-treated with corticosteroids, antihistamines, and H_2 antagonists.**
- **Should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3.**

BEFORE you use PACLITAXEL INJECTION, USP always talk to your doctor or pharmacist especially if:

- you have or have had any of the following medical conditions:
  - liver disease
  - heart problems
  - any blood disorder with a reduced number of red blood cells, white blood cells, or platelets
  - any disease of the nerves
  - lowered immunity due to diseases such as HIV/AIDS
  - lowered immunity due to treatment with medicines such as cyclosporin, or other medicines used to treat cancer (including radiation therapy)
- you are pregnant or plan to become pregnant
- you are breast-feeding or plan to breast-feed
- you have any allergies to this drug or its ingredients
- you are receiving radiation therapy
- you have experienced symptoms of pseudomembranous colitis (severe or persistent diarrhea that may be watery or bloody, abdominal cramps, fever, pus or mucous in your stool, nausea)
- you have experienced symptoms of mucositis (red or swollen mouth and gums, blood or sores in mouth, soreness or pain in mouth or throat, difficulty swallowing or talking, feeling of dryness or pain while eating)

INTERACTIONS WITH THIS MEDICATION

Paclitaxel for Injection interacts with other drugs. Before therapy, talk to your doctor if you are using any other medications (prescription, non-prescription or herbal remedies).

Drugs that may interact with Paclitaxel for Injection include: cisplatin, doxorubicin cimetidine, ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, vincristine, testosterone, 17 α -ethinyl estradiol, retinoic acid, quercetin, deferasirox, and trimethoprim.

The herbal remedy, St. John's Wort may also interact with paclitaxel.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will decide what dose of Paclitaxel for Injection you will receive. This depends on your condition and other factors, such as your weight and other chemotherapy medicines you are being given.

If you are being treated for Kaposi's sarcoma, **PACLITAXEL INJECTION, USP** will be administered at a dose of 135mg/m² with a three week interval between courses or 100mg/m² with a two week interval between courses.

Before you are given Paclitaxel for Injection, you must take some other medicines to prevent allergic reactions occurring during your treatment. You will need to take dexamethasone tablets 12 hours and six hours before your treatment, which your doctor will prescribe for you. You will also be given two different injections 30 to 60 minutes prior to receiving Paclitaxel for Injection. This will minimize the risk of allergic reactions occurring.

Several courses of Paclitaxel for Injection therapy may be needed depending on your response to treatment.

Additional treatment may not be repeated until your blood cell numbers return to acceptable levels and any uncontrolled effects have been controlled. Your doctor will decide.

Overdose:
As Paclitaxel for Injection is given to you under the supervision of your doctor, it is very unlikely that you will receive too much. However, if you experience severe side effects after being given this medicine, tell your doctor or nurse immediately. You may need urgent medical attention.

Symptoms of overdose include the side effects listed below in the 'Side Effects' section but are usually of a more severe nature.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Tell your doctor if you notice any of the following and they worry you:

- muscle or joint pain on the arms and legs
- nausea and vomiting
- hair loss
- diarrhoea
- changes in skin or nail appearance
- soreness or ulceration of the mouth.

The above list includes the more common side effects of your medicine.

In addition, you should have a complete eye and vision examination in case of vision problems. If cystoid macular edema (blurred vision due to swelling of the retina within the eye) is diagnosed, your doctor may stop your treatment.

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 get immediate medical help.
		Only if severe	In all cases	
Common	• pain, swelling, irritation and redness at the injection site	√		
	• flushing	√		
	• light-headedness, dizziness or fainting (due to low blood pressure)	√		
	• numbness or tingling in the fingers and / or toes	√		
	• changes in vision	√		
	• abdominal pain	√		
	• shortness of breath, wheezing or difficulty breathing		√	
	• swelling of the face, lips, tongue, or other parts of the body		√	
	• rash, itching or hives on the skin		√	
	• extreme weakness or tiredness		√	
	• seizures (fits)		√	
	• fast, slow or irregular heart beat		√	
	• chest pain		√	
	• yellowing of the skin or eyes		√	
	• unusual bleeding or bruising (including blood in your stools or urine)		√	
	• fever, sore throat or other signs of infection.		√	
Uncommon	• myocardial			√

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 get immediate medical help.
		Only if severe	In all cases	
	infarction (severe chest pains possibly radiating to the jaw or arm, sweating, breathlessness and nausea)			
	• grand mal seizures (loss of consciousness and violent muscle contractions), ataxia (lack of muscle group),		√	
	• encephalopathy (effect on the brain)			√
	• Cardiomyopathy (a disease of the heart muscle)			√
	• pseudomembranous colitis (severe or persistent diarrhea that may be watery or bloody, abdominal cramps, fever, pus or mucous in your stool, nausea)		√	
	• acute myeloid leukemia or myelodysplastic syndrome (fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool)			√
	• tumor lysis syndrome (nausea, shortness of breath, irregular heartbeat, cloudy urine, tiredness, or pain in joints)			√
	• respiratory failure (sudden worsening or shortness of breath, bluish color on skin, lips, and fingernails, irregular heartbeats, feel sleepy, loss of consciousness)			√
	• erythema multiforme (rapid formation of a rash followed by the appearance of skin lesions that start on the backs of hands and tops of feet before spreading to the trunk)		√	
	• dermatitis exfoliative (severe skin peeling)			√
	• systemic lupus erythematosus (an autoimmune disorder that may affect your skin, joints, kidneys, brain, and other organs)			√
	• sclerodema (hardening of the skin and connective tissues (the fibers that provide the framework and support for your body)			√

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

HOW TO STORE IT

PACLITAXEL INJECTION, USP will be stored in the pharmacy or on the ward. The injection should be stored at room temperature (15-30°C). Retain in the original package and protect from light.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffectcanada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at www.mylan.ca.

This full Product Monograph prepared for health professionals, can be obtained by contacting the sponsor Mylan Pharmaceuticals ULC at 1-844 596-9526.

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