PRODUCT MONOGRAPH

PrPACLITAXEL FOR INJECTION USP

6 mg/mL

Sterile Solution for Injection

ANTINEOPLASTIC AGENT

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous	Solution for Injection, 6 mg/mL	Anhydrous Ethanol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Paclitaxel for Injection USP is indicated, alone or in combination, for the treatment of carcinoma of the ovary, breast, lung, or AIDS-related Kaposi's Sarcoma.

Ovarian Carcinoma

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

Breast Carcinoma

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

Paclitaxel for Injection USP is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Polyoxyl 35 Castor Oil.

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- 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 USP should be administered as diluted infusion.
- Patients should be pre-treated with corticosteroids, antihistamines, and H2 antagonist (see **Sensitivity/Resistance** section below).
- Should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm3 or have AIDS-related Kaposi's Sarcoma with a baseline or subsequent neutrophil counts of less than 1,000 cells/mm3 (see **Hematologic** section below).

General

Paclitaxel for Injection USP 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 for Injection USP solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Carcinogenesis and Mutagenesis

See section **TOXICOLOGY** under **SCIENTIFIC INFORMATION**.

Cardiovascular

Hypotension, hypertension and bradycardia have been observed during Paclitaxel for Injection USP administration; patients are usually asymptomatic and generally do not require treatment. In severe cases, Paclitaxel for Injection USP infusions may need to be interrupted or discontinued at the discretion of the treating physician. Frequent monitoring of vital signs, particularly during the first hour of Paclitaxel for Injection USP 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 for Injection USP.

Driving/Operating Machinery

Since Paclitaxel for Injection USP contains ethanol, consideration should be given to the possibility of CNS and other effects.

Hematologic

Paclitaxel for 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 for Injection USP. Patients should not be retreated with subsequent cycles of Paclitaxel for 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 for 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 for 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 for 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 erythema, tenderness, skin discolouration, or swelling at the injection

site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., “recall”, has been reported rarely.

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

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

Neurologic

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

Paclitaxel for Injection USP contains anhydrous ethanol, 396 mg/mL; consideration should be given to possible CNS and other effects of ethanol. Children may be more sensitive than the adults to the effects of ethanol (see **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 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 USP should be administered as a diluted infusion. Patients receiving Paclitaxel for Injection USP should be pretreated with corticosteroids, antihistamines, and H_2 antagonists (such as dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions (see **DOSAGE AND ADMINISTRATION**).

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, or generalized urticaria have occurred in approximately 2% of patients receiving paclitaxel. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pretreatment. In case of a severe hypersensitivity reaction, Paclitaxel for Injection USP 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 Polyoxyl 35

Castor Oil should not be treated with Paclitaxel for 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 for Injection USP and aggressive symptomatic therapy.

Special Populations

Pregnant Women: Paclitaxel for 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 for Injection USP. If Paclitaxel for 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 for Injection USP is excreted in human milk. Breast feeding should be discontinued for the duration of Paclitaxel for Injection USP therapy.

Pediatrics: The safety and effectiveness of Paclitaxel for Injection USP in pediatric patients have not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of Paclitaxel for Injection USP for use in this population.

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, 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 CLIN**ICAL TRIALS: AIDS-Related Kaposi's Sarcoma**). 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/mm^3 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 3 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 phosphatase 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 incidences of adverse reactions in the table that follows are derived from ten clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated with single-agent paclitaxel at doses ranging from 135-300 mg/m^2/day and schedules of 3 or 24 hours. Data from a subset of 181 patients treated at the recommended dose of 175 mg/m^2 and a 3-hour infusion schedule is also included in the table.

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/m^2/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/mm^3	90	87
	< 500/mm^3	52	27
Leukopenia	< 4,000/mm^3	90	86
	< 1,000/mm^3	17	4
Thrombocytopenia	< 100,000/mm^3	20	6
	< 50,000/mm^3	7	1

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

Safety referring to a large randomized trial of paclitaxel (135 mg/m^2 over 24 hours) / cisplatin (75 mg/m^2) versus cyclophosphamide/cisplatin, including 410 patients (196 receiving paclitaxel), has been evaluated. The combination of paclitaxel with platinum agents has not resulted in any clinically relevant changes to the safety profile of the drug when used at the recommended dosage.

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

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

Unless otherwise stated, the following safety data relate to 62 patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m^2 and a 3-hour infusion schedule, in phase III clinical trials. All patients were premedicated to minimize hypersensitivity reactions. Data from these clinical trials demonstrate that paclitaxel given at this dose and schedule is well tolerated. Bone marrow suppression and peripheral neuropathy were the principle dose-related adverse effects associated with paclitaxel. Compared to 24-hour infusion schedules, neutropenia was less common when paclitaxel was given as a 3-hour infusion. Neutropenia was generally rapidly reversible and did not worsen with cumulative exposure. The frequency of neurologic symptoms increases with repeated exposure.

None of the observed toxicities were influenced by age.

AIDS-related KAPOSI'S SARCOMA

The following table shows the frequency of important adverse events in the 85 patients with 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]		

	Percent of Patients	
	Study CA139-174 135/3[b]/3 wk (n = 29)	Study CA139-281 100/3 [b]/2 wk (n = 56)
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
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 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 tumours treated with single-agent paclitaxel in 10 clinical studies. Toxicities that occurred with greater severity or frequency in previously untreated patients with ovarian carcinoma or NSCLC who received paclitaxel in combination with cisplatin or in patients with breast cancer who received paclitaxel after doxorubicin/cyclophosphamide in the adjuvant setting, or in patients with AIDS-related Kaposi's Sarcoma, and that occurred with a difference that was clinically significant in these populations are also described. In addition, rare events have been reported from postmarketing experience or from other clinical studies.

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

Hematologic

The most frequent significant undesirable effect of paclitaxel was bone marrow suppression. Neutropenia was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (<500 cells/mm^3) occurred in 27% of patients treated at a dose of 175 mg/m^2, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days or more. Neutropenia was not more frequent or severe in patients who received prior radiation therapy, nor did it appear to be affected by treatment duration or cumulative exposure.

When paclitaxel was administered to patients with ovarian carcinoma at a dose of 175 mg/m^2/3 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of severe neutropenia and of febrile neutropenia were similar in the paclitaxel plus cisplatin arm and in the control arm.

When paclitaxel was administered in combination with cisplatin to patients with advanced NSCLC in the Eastern Cooperative Oncology Group (ECOG) study, the incidence of neutropenia (Grade IV) was 74% (paclitaxel 135 mg/m^2/24 hours plus cisplatin) and 65% (paclitaxel 250 mg/m^2/24 hours plus cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide. Considerably less Grade IV neutropenia was observed in the European Organization for Research and Treatment of Cancer (EORTC) (28%) and CA139-208 (45%) studies for paclitaxel 175 mg/m^2/3 hours plus cisplatin (without G-CSF).

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% of the patients given 135 mg/m^2 and 26% of the patients given 175 mg/m^2 by a 3-hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's Sarcoma, 61% of the patients reported at least one opportunistic infection. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See **DOSAGE AND ADMINISTRATION**).

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

received platelet transfusions. In the adjuvant breast carcinoma trial, the incidence of severe thrombocytopenia and platelet transfusions increased with higher doses of doxorubicin.

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

Hypersensitivity Reactions (HSR)

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

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

Cardiovascular

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

Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement. The incidence of Grade III or greater cardiovascular events was 13% (paclitaxel 135 mg/m^2/24 hours plus cisplatin), 12% (paclitaxel 250 mg/m^2/24 hours plus cisplatin and G-CSF), and 6% (paclitaxel 175 mg/m^2/3 hours plus cisplatin) when paclitaxel followed by cisplatin was administered to patients with advanced NSCLC; there was a similar incidence in the non-paclitaxel control arms. The apparent increase in these cardiovascular events in patients with NSCLC compared to patients with breast or ovarian cancer is possibly related to the difference in cardiovascular risk factors among patients with lung cancer.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECG at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

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 2 to 10. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. In the Intergroup first-line ovarian carcinoma study, the regimen with paclitaxel 175 mg/m2 by 3-hour infusion followed by cisplatin 75 mg/m2 resulted in greater incidence and severity of neurotoxicity (reported as neuromotor or neurosensory events) than the regimen containing cyclophosphamide 750 mg/m2 followed by cisplatin 75 mg/m2 , 87% (21% severe) versus 52% (2% severe), respectively. In the GOG first-line ovarian carcinoma study, the regimen with paclitaxel (135 mg/m^2 over 24 hours) followed by cisplatin (75 mg/m^2) resulted in an incidence of neurotoxicity (reported as peripheral neuropathy) that was similar to the regimen containing cyclophosphamide 750 mg/m^2 followed by cisplatin 75 mg/m^2, 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in Intergroup and GOG trials suggests that when paclitaxel is given in combinations with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m^2 given by 3-hour infusion (21%) than at a dose of 135 mg/m^2 given by 24-hour infusion (3%). In patients with NSCLC, administration of paclitaxel followed by cisplatin resulted in greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent paclitaxel. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving paclitaxel 135 mg/m^2 by 24-hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide.

Arthralgia/myalgia

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

Alopecia

Alopecia was observed in almost all patients.

Gastrointestinal

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

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

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

Hepatic

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

Renal

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

Injection Site Reactions

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discolouration, or swelling at the injection

site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-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 discolouration 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/m2 over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/ cisplatin.

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 coadministration 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
Cardiovascular: Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.
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.
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.
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.
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. Postmarketing reports of ototoxicity (hearing loss and tinnitus) have been received.
Opthalmologic: There have been reports of reduced visual acuity due to cystoid macular edema (CME) during treatment with Paclitaxel (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: Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism, have been received as part of the continuing surveillance of paclitaxel safety.
Other: Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been received as part of the continuing surveillance of paclitaxel safety.
Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.

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 USP should be given

before cisplatin when used in combination.

Cimetidine

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

Substrates, Inducers, Inhibitors of Cytochrome P450 2C8 and 3A4
The metabolism of Paclitaxel for Injection USP is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering Paclitaxel for 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, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, montelukast and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Potential interactions between Paclitaxel for Injection USP, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials. Caution and close monitoring of liver function is required; further, no unapproved (e.g., investigational) protease inhibitor should be administered with Paclitaxel for Injection 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 USP and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and 3-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Drug-Drug Interactions

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	Decrease in paclitaxel clearance when paclitaxel was administered following	Paclitaxel for Injection should be given before cisplatin when used in combination.

		cisplatin	
Cimetidine	CT	No effect	The clearance of paclitaxel was not affected by cimetidine pre-treatment.
Ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, vincristin, testosterone, 17α-ethinyl estradiol, retinoic acid, montelukast, quercetin	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
Interactions with herbal products have not been established.

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

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Metastatic carcinoma of the ovary

The administration of Paclitaxel for Injection USP at a dose of 175 mg/m^2 over 3 hours in combination with cisplatin 75 mg/m^2 every 3 weeks is recommended for the primary treatment of patients with advanced carcinoma of the ovary. Paclitaxel for Injection 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 3 hours every 3 weeks.

Carcinoma of the breast

For the adjuvant treatment of node-positive breast cancer, the recommended regimen is Paclitaxel for Injection USP, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for four courses administered sequentially to standard combination therapy. After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, Paclitaxel for Injection USP at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

Non-small cell lung carcinoma

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

Single courses of Paclitaxel for 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 for Injection USP therapy should have the dosage reduced by 20% for subsequent courses of Paclitaxel for Injection USP.

AIDS-related Kaposi's Sarcoma

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

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

1. the dose of dexamethasone as one of the three premedication drugs should be reduced to 10 mg orally.
2. treatment with Paclitaxel for Injection 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 for 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.

Administration

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

Paclitaxel for 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 premedicated prior to Paclitaxel for Injection USP administration

in order to reduce the risk of severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and 6 hours before Paclitaxel for Injection USP, diphenhydramine 50 mg I.V. (or its equivalent), 30 to 60 minutes prior to Paclitaxel for Injection USP, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before Paclitaxel for Injection USP.

Preparation Precautions

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

If Paclitaxel for Injection USP 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 Concentration**
5 mL	0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection	100 mL	non-PVC infusion bags (ie., Polyolefin bag) or Glass Bottles	0.3 mg/mL
20 mL				1.2 mg/mL

[1]Prior to the addition of drug, calculate the approximate 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 for Injection USP must be diluted prior to infusion. Paclitaxel for 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 15 to 30°C (protect from light); infusions should be completed within this timeframe. There have been rare reports of precipitation with longer than the recommended 3-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel for Injection 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 for Injection USP since they can cause the stopper to collapse resulting in loss of sterile integrity of Paclitaxel for Injection USP solution

OVERDOSAGE

There is no known antidote for Paclitaxel for Injection USP 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).

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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, nonfunctional 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 tumour 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 PHARMACOLOGY**).

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.

	t½ (h)	Clearance	Volume of distribution
dose mean	3.0 to 52.7 hours	11.6 to 24.0 L/h/m2	198 to 688 L/m2

Absorption: The pharmacokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m^2 and infusion schedules ranging from 3 to 24 hours. Following intravenous administration of paclitaxel, the drug exhibited a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3.0 to 52.7 hours, and total body clearance has ranged from 11.6 to 24.0 L/h/m^2. Mean steady state volume of distribution has ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

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

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 µg/mL, indicated that on average 89% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Metabolism: *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (see **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 3-hour infusion, 14% of the radioactivity was recovered in the urine and 71% was

excreted in the feces in 120 hours. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance.

STORAGE AND STABILITY

Paclitaxel for Injection USP should be stored at room temperature (15-30°C). Retain in the original package and protect from light. Once punctured, the 5, 16.7, and 25 mL vials of Paclitaxel for Injection USP are stable for 28 days at room temperature. The 50 mL pharmacy bulk vial should be used within 24 hours after initial entry. Discard unused portion.

Solutions for infusion are physically and chemically stable for up to 27 hours at 15 to 30°C (protect from light); infusions should be completed within this timeframe. Discard unused portion.

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, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

PREPARATION FOR INTRAVENOUS ADMINISTRATION

Contact of undiluted Paclitaxel for Injection USP 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 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.

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

Paclitaxel for Injection USP should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

SPECIAL INSTRUCTIONS

1. Preparation of Paclitaxel for Injection USP should be done in a vertical laminar flow

hood (Biological Safety Cabinet - Class II).

2. Personnel preparing Paclitaxel for Injection USP should wear PVC gloves, safety glasses, disposable gowns and masks.
3. All needles, syringes, vials and other materials which have come in contact with Paclitaxel for Injection 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.
4. Personnel regularly involved in the preparation and handling of Paclitaxel for Injection USP should have bi-annual blood examinations.
5. Directions for Dispensing from Pharmacy Bulk Vial The use of Pharmacy Bulk Vial is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. Dispensing from the Pharmacy Bulk Vial should be completed within 24 hours after initial entry.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Paclitaxel for Injection USP is available in multidose vials of 5 mL, 16.7 mL and 25 mL and pharmacy bulk vial of 50 mL containing respectively 30 mg, 100 mg, 150 mg and 300 mg paclitaxel at a concentration of 6 mg/mL. All vial sizes are available in cartons of 1 vial.

Each mL of Paclitaxel for Injection USP contains paclitaxel 6 mg, Polyoxyl 35 Castor Oil 527 mg and Anhydrous Ethanol 396 mg.

PART II: SCIENTIFIC INFORMATION

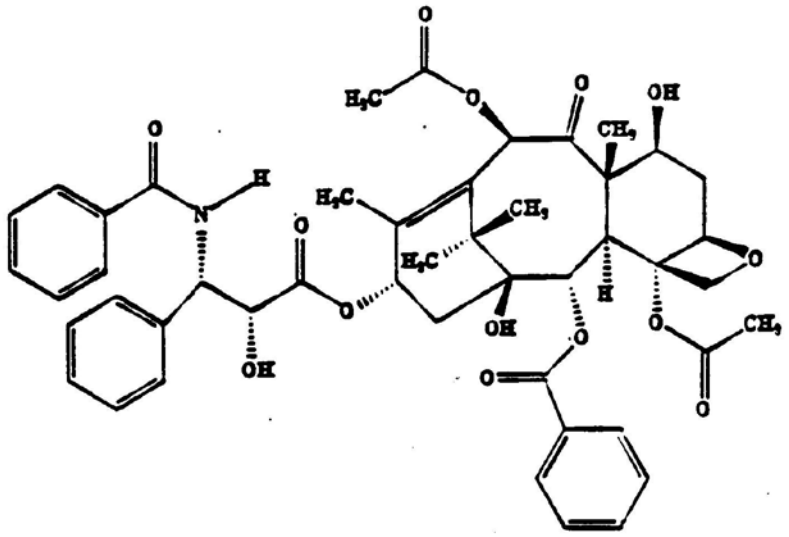
PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Proper Name: Paclitaxel

Chemical Name: 5ß,20-epoxy-1,7ß-dihydroxy-9-oxotax-11-ene-2α,10β,13α-tetrayl 4,10-diacetate 2-benzoate 13-[(2R,3S)-3-(benzoylamino)-2-hydroxy-3-phenylpropanoate

Structural Formula:



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

Molecular Mass: 853.9

Physicochemical properties: Paclitaxel is a white or almost white crystalline powder, practically insoluble in water, soluble in methanol and freely soluble in methylene chloride.

CLINICAL TRIALS

Ovarian Carcinoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
First-Line data: Phase 3 multicenter, randomized, controlled trial conducted by GOG, comparing therapy with paclitaxel (P) in combination with cisplatin (c) to cyclophosphamide (AC) in combination with cisplatin (c)	-135 mg/m^2 of P over 24 hrs + 75 mg/m^2 of c - 750 mg/m^2 of AC + 75 mg/m^2 of c	410	Stage III or IV disease (> 1 cm residual disease after staging laparotomy or distant metastases) with no prior chemotherapy	Patients treated with P in combination with cisplatin has significantly longer time to progression (median 16.6 vs. 13.0 months, p = 0.0008) and nearly a year longer median survival time (p = 0.0002) compared with standard therapy.
Second-Line data: Phase 3 multicenter , bifactorial, randomized trial comparing two dosage regimens of paclitaxel (P) irrespective of the schedules and two schedules irrespective of dose.	- 175 mg/m^2 of P over 24 hrs - 175 mg/m^2 of P over 3 hrs - 135 mg/m^2 of P over 24 hrs - 135 mg/m^2 of P over 3 hrs	407	Patients (pts) who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary.	Pts receiving the 175 mg/m^2 dose had a response rate (RR) similar to that for those receiving the 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in RR was detected when comparing the 3-hr with the 24-hr infusion: 15% vs. 17% (p=0.50). Pts receiving the 175 mg/m^2 dose of P had a longer time to progression (TTP) than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months (p=0.03). The median TTP for pts receiving the 3-hour vs. the 24-hr infusion were 4.0 months vs. 3.7 months, respectively. Median survival was 11.6 months in pts receiving the 175 mg/m^2 dose of P and 11.0 months in pts receiving the 135 mg/m^2 dose (p=0.92). Median survival was 11.7 months for pts receiving the 3-hr infusion of P and 11.2 months for pts receiving the 24-hr infusion (p=0.91).

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

Second -Line data: In addition to the Phase 3 trial described above, data from five Phase 1 and 2 clinical studies as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of paclitaxel in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Paclitaxel remained active in patients who had developed resistance to platinum-containing therapy (defined as tumour progression while on, or tumour relapse within 6 months from completion of, a platinum containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 & 2 clinical studies. The adverse event profile in this Phase 3 study was consistent with that seen in previous clinical studies (see ADVERSE REACTIONS).

The results of this randomized study support the use of paclitaxel at doses of 135 to 175 mg/m^2, administered by a 3-hour intravenous infusion. The same doses administered by 24-hour infusion were more toxic.

Breast Carcinoma

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
Adjuvant Breast Carcinoma Study: Phase 3 multicenter, 3X2 factorial, randomized trial, conducted by CALGB, ECOG, NCCTG and SWOG, comparing adjuvant therapy with paclitaxel (P) to no further chemotherapy following four courses of doxorubicin (A) and cyclophosphamide (C)	600 mg/m^2 of C + A at doses of either -60 mg/m^2 (on day 1), - 75 mg/m^2 (in two divided doses on days 1 and 2), or - 90 mg/m^2 (in two divided doses on days 1 and 2 with prophylactic G-CSF support and ciprofloxacin) every 3 weeks for four courses and either - 175 mg/m^2 of P over 3 hrs every 3 weeks for four additional courses or - no additional chemotherapy. Patients (pts) whose tumours were +ve were to receive subsequent tamoxifen (20 mg daily for 5 years); patients who received segmental mastectomies prior to study were to receive breast irradiation after recovery from treatment-related toxicities.	3170	Node-positive breast carcinoma following either mastectomy or segmental mastectomy and nodal dissections.	Median follow-up was 30 .1 months. Of 2066 pts who were hormone receptor positive, 93% received tamoxifen. Based on a multivariate Cox model for disease- free survival, pts on AC + P had 22% risk reduction of disease recurrence compared to pts on AC (Hazard Ratio [HR] = 0.78, 95% CI 0.67-0.91, p = 0.0022) and 26% reduction in the risk of death (HR = 0.74, 95% CI 0.60-0.92, p = 0.0065). Increasing the dose of A higher than 60 mg/m^2 had no effect on either disease-free survival or overall survival. Subset analyses including number of positive lymph nodes, tumour 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 tumours had a smaller reduction in hazard (HR = 0.92) for disease-free survival with P than other groups.

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
After Failure of Initial Chemotherapy: Phase 3 multicenter, randomized trial comparing two dosage regimens of paclitaxel (P).	- 175 mg/m^2 of P over 3 hrs - 135 mg/m^{2}of P over 3 hrs	471	Patients (pts) who failed chemotherapy either in the adjuvant (30%) or metastatic (39%) setting or both (31%). At study entry, 60% had symptomatic disease with impaired performance status and 73% had visceral metastases.	The overall response rate was 26% (95% Cl: 22 to 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4-18.1 + months). Overall, the median time to progression was 3.5 months (range: 0.03-17.1 months). Median survival was 11.7 months (range: 0-18.9 months).

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

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

Non-Small Cell Lung Carcinoma (NSCLC)

Study Design	Treatments / Doses	No. of Patients	Population	Endpoints/Conclusion
Phase 3 multicenter, open label, randomized trial conducted by ECOG, comparing two dosage regimens of paclitaxel (P) in combination with cisplatin (c) to cisplatin (c) followed by etoposide (VP)	-135 mg/m^2 of P over 24 hrs + 75 mg/m_2 of c - 250 mg/m^2 of P over 24 hrs + 75 mg/m^2 of c with G-CSF support -75 mg/m^2 of c on day 1 followed by 100 mg/m^2 of VP on days 1, 2 and 3 (control)	599	Non-Small Cell Lung Cancer	There were statistically significant differences favouring each of the P plus c arms for response rate and time to tumour progression. There was no statistically significant difference in survival between either P plus c arm and the c plus VP arm. In this study, the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire had seven subscales that measured subjective assessment of treatment. Of the seven, the Lung Cancer Specific Symptoms subscale favoured P at 135 mg/m^2 of P as a 24-hr infusion + 75 mg/m^2 of c. For all other factors, there was no difference in the treatment groups.

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

AIDS-Related Kaposi's Sarcoma

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

All patients had widespread and poor-risk disease. Applying the ACTG staging criteria to patients with prior systemic therapy, 93% were poor risk for extent of disease (T1), 88% had a CD4 count <200 cells/mm^2 (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 tumour 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 Tumour 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 tumours (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 tumours. (See **ADVERSE REACTIONS**).

DETAILED PHARMACOLOGY

In vitro

Paclitaxel exhibits cytotoxic activity against a wide variety of both human and rodent tumour 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 tumour necrosis factor-α (TNF-α) accompanied by down regulation of the receptor.

In Vivo

Paclitaxel has shown antitumour activity against many tumour models including leukemias and solid tumours and human solid xenografts. The table that follows summarizes paclitaxel's activity.

Tumour, Site	Form	Route	Activity
MURINE LEUKEMIAS			
L1210, ip	*	ip	Borderline → modest
P388, ip	*	ip	Mild
P1534, ip	*	ip	Mild → substantial
MURINE SOLID TUMOURS			
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 TUMOUR 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)**].
Mouse/CD2F$_1$	10 10 10 10 10 10 10 10 10 10	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	1/2 LD_{10}, LD_{10} and LD_{50} dose groups: Necrosis of developing spermatocytes. Giant cell formation. LD_{10} and LD_{50} dose groups: Decrease in reticulocyte and neutrophil values. Lower liver and testicular weights. Moderate to severe thymic cortical lymphoid depletion. Necrosis or atrophy of small intestinal mucosa and crypt cell hypoplasia. Neurophilic hyperplasia, eosinopenia, lymphoid hypoplasia and atypical megakaryocytes, deaths (2/10 M, 8/10 F at LD_{10}; 8/10 M, 9/9 F at LD_{50}). All dose groups: Dose-related decreased body weight, lethargy, rapid respiration, rough coat, thin/hunched posture, hypothermia, squinted eyes with exudate.

SUBACUTE TOXICITY (cont'd)

Species/Strain	No./ Group	Sex	Dose Range[a] mg/kg/day	Route	Duration	Drug Related Findings
Rat/Sprague-Dawley	10 10 10 10 10 10 10 10 10 10	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 reticulocyte counts, white foci in submandibular lymph nodes and/or salivary glands.
Dog/Beagle	1 1	M F	0, 0.375, 0.75, 1.5, 3.0, 6.0	iv	5 Days	All doses: Decreased body weight. Increased ALT, cholesterol, triglycerides and total lipids. Intestinal hemorrhage or agonal changes. Lymphoid depletion of tonsils and/or bronchial lymph node. $\geq$1.5 mg/kg/day: Marked decreases in leukocyte, reticulocyte, platelet, and erythrocyte counts. $\leq$1.5 mg/kg/day: Moderate to severe bone marrow hematopoietic hypoplasia. 3.0 to 6.0 mg/kg/day: Deaths (All)

* Range Finding phase ** Lethality phase

[a] Paclitaxel dissolved in Cremophor† EL (50%): ethanol (50%) and then diluted with saline to provide dosing solutions

[b] Untreated

CHRONIC TOXICITY

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

*Paclitaxel dissolved in Cremophor† EL (50%): ethanol (50%) and then diluted with saline to provide dosing solutions

REPRODUCTION AND TERATOLOGY

Species/ Strain	No./ Group	Sex	Route	Dose* and Frequency	Drug Related Findings
SEGMENT I Rat/Sprague-Dawley	20 20 20	M F F	iv	0 (vehicle), 0 (saline) 0.1, 0.3, 1.0 mg/kg M: 63 days prior to mating and during mating F: During mating and through day 7 of gestation 0 (Non-treated)	Body weight gain and food intake were lower in F_0 males and females Days 25-63 and Days 28-62, respectively, of premating period. Body weight gain and food intake were lower in F_0 females during Days 2-20 of gestation at the high dose level. Fertility indices in the F_0 generation were lower at 1 mg/kg/day compared to saline and vehicle control groups. Copulation indices were similar to control. Adrenal, uterine and ovarian weights lower in F_0 dams compared to controls. Numbers of corpora lutea, implantations and live fetuses were decreased, and numbers of empty implantation sites and fetal deaths were increased at 1 mg/kg/day. The no-effect dose was 0.3 mg/kg/day in both F_0 and F_1 generations.
SEGMENT II Rabbit/New Zealand White	20	F	iv	O (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 dissolved in Cremophor† EL (50%): ethanol (50%) and then diluted with saline to provide 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 for Injection USP
6 mg/mL
Sterile Solution for Injection

This leaflet is part III of a three-part "Product Monograph" published when Paclitaxel for 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 for 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 medicines containing Polyoxyl 35 Castor Oil, 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:
Polyoxyl 35 Castor Oil and Anhydrous Ethanol.

What dosage forms it comes in:
Solution for injection, 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 or have AIDS-related Kaposi's Sarcoma with a baseline or subsequent neutrophil counts of less than 1,000 cells/mm^3**

BEFORE you use Paclitaxel for Injection USP 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 plan to become pregnant
- you have any allergies to this drug or its ingredients
- you are receiving radiation therapy

INTERACTIONS WITH THIS MEDICATION

Paclitaxel for Injection USP 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, vincristin, testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin.

PROPER USE OF THIS MEDICATION

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

Before you are given Paclitaxel for Injection USP, 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 USP. 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 USP 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 call your doctor or pharmacist
		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 infarction		✓	
	•grand mal seizures, ataxia, encephalopathy		✓	

This is not a complete list of side effects. For any unexpected effects while taking Paclitaxel for Injection USP, contact your doctor or pharmacist.

HOW TO STORE IT

Paclitaxel for Injection USP should be stored at room temperature (15-30°C). Retain in the original package and protect from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.sterimaxinc.com

or by contacting the sponsor, SteriMax Inc., at:
1-800-881-3550

This leaflet was prepared by SteriMax Inc.

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