PRODUCT MONOGRAPH

PAXENE™
(paclitaxel for injection concentrate)

6 mg/mL

antineoplastic agent

Date of Preparation: March 21, 2000

Date of Revision: January 31, 2006

IVAX Research, Inc.
Miami, Florida

Control Number: 102716

PRODUCT MONOGRAPH

PAXENE™
(paclitaxel for injection concentrate)

6 mg/mL

THERAPEUTIC CLASSIFICATION

antineoplastic agent

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

Patients receiving PAXENE should be pre-treated with corticosteroids, diphenhydramine, and H_2 antagonists in order to minimize hypersensitivity reactions (see DOSAGE AND ADMINISTRATION section). Severe hypersensitivity, which may be characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria, occurred rarely in patients receiving PAXENE. A fatal reaction was reported in a patient treated with another paclitaxel-containing product, without premedication. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with PAXENE.

PAXENE therapy should not be given to patients with baseline neutrophil counts of less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving PAXENE.

ACTIONS AND CLINICAL PHARMACOLOGY

PAXENE (paclitaxel) is a natural product with antitumor activity.

Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the

normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

Information on the *in vitro* and *in vivo* antitumor activity of paclitaxel is found in the PHARMACOLOGY section.

The pharmacokinetics of paclitaxel following administration of 100 mg/m^2 Paxene dose given over 3 hours to 19 patients with AIDS-related Kaposi's sarcoma was studied. The mean values for the peak plasma concentration and AUC were 1.5 μg/mL and 5.6 μg·h/mL, respectively. The total body clearance and elimination half-life values were 20.5 L/h/m^2 and 23.7.

In vitro studies of binding of paclitaxel to human serum proteins using paclitaxel concentrations of 0.1 to 50 μg/mL indicate that between 89-98% is bound; the presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

Following intravenous Paxene 175 mg/m^2 given over 3 hours in 20 patients (14 females, 6 males) with a mean age of 53 years with the majority diagnosed with advanced ovarian or breast carcinoma and none with AIDS-KS, about 7% of the dose was excreted in the urine and there was evidence of extensive hepatic metabolism. In 6 of these patients, about 10% of the administered dose recovered in the feces over 72 hours was unchanged paclitaxel, while metabolites, primarily 6-α-hydroxypaclitaxel accounted for the balance. As noted in the literature *in vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6-α-hydroxypaclitaxel by cytochrome P450 2C8 and to 3'-p-hydroxypaclitaxel by CYP3A4.

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 CYP3A4. (See PRECAUTIONS). The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

For further information regarding clinical pharmacology of PAXENE, see PHARMACOLOGY section.

Clinical Studies

In an open-label, non-comparative phase II clinical study, 107 patients with advanced Kaposi's sarcoma were administered a dose of 100 mg/m^2 PAXENE as a 3 hour infusion every 2 weeks. All patients had received and failed initial and subsequent systemic chemotherapy prior to enrollment in the study and 63 patients (59%) had progressive disease on treatment with liposomal anthracyclines

(core patients). All patients had widespread and "poor risk" disease. The response rates were 57% in core patients. The median time to response was 49 days; the median duration of response measured from first day of treatment was 292 days. The median time to disease progression was estimated to be 468 days and the median survival time was >617 days (lower 95% CI bound; median not reached).

The response rates were similar in patients who either received or did not receive protease inhibitors during the first 10 cycles of Paxene.

Other benefits observed in some patients include instances of improved pulmonary symptoms in patients with pulmonary involvement, improved ambulation, resolution of ulcers and resolution of facial lesions and edema in patients with KS involving the face, extremities and genitalia. However, these data were based on small patient numbers.

Filgrastim (G-CSF) was required by 60% of patients at any time during the first 15 cycles. About 3% of patients discontinued treatment due to toxicity and 12% of patients required dose-reduction due to toxicity.

INDICATIONS AND CLINICAL USE

PAXENE (paclitaxel) is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma, who have failed prior liposomal anthracycline therapy.

CONTRAINDICATIONS

PAXENE (paclitaxel) is contraindicated in patients who have a history of hypersensitivity reactions to PAXENE or other paclitaxel-containing products or other drugs formulated in polyoxyl 35 castor oil. Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g., cyclosporin for injection concentrated and teniposide for injection concentrate) should not be treated with PAXENE. Patients who have developed severe hypersensitivity reactions should not be rechallenged with PAXENE.

Furthermore, available clinical data do not support the use of PAXENE in patients with severe hepatic impairment, pre-treatment neutropenia less than 1,000 cells/mm^3, concurrent, serious and uncontrolled infection, pregnancy or lactation.

WARNINGS

Patients should be pretreated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine) before receiving PAXENE (paclitaxel) (see "DOSAGE AND ADMINISTRATION" section). Severe hypersensitivity reactions, which may be characterized by dyspnea and hypotension requiring treatment, angioedema and generalized urticaria, have occurred in < 3% of patients receiving PAXENE. These reactions are probably histamine-mediated. Patients who experience severe hypersensitivity reactions to PAXENE or TAXOL should not be rechallenged with PAXENE.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occur at a median of 13-14 days. PAXENE should not be administered to patients with baseline neutrophil counts of less than 1,000 cells/mm^3. Frequent monitoring of blood counts should be instituted during PAXENE treatment. Patients should not be re-treated with subsequent cycles of PAXENE until neutrophils recover to a level >1,000 cells/mm^3 and platelets recover to a level >75,000 cells/mm^3.

If patients develop significant conduction abnormalities during PAXENE infusion, appropriate therapy should be administered and continuous cardiac monitoring is recommended during subsequent therapy with PAXENE.

Pregnancy

PAXENE may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryo- and feto-toxic in rats and rabbits and to decrease fertility in rats. In these studies, paclitaxel was shown to result in abortions, decreased corpora lutea, a decrease in implantations and live fetuses, and increased resorptions and embryo-fetal deaths. Fetal abnormalities included increased incidence of multiple skeletal malformations and marked dilation of the lateral ventricles of the brain.

There are no studies in pregnant women. If Paxene is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient should be advised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted PAXENE (paclitaxel) solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

PAXENE 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.

Drug Interactions: The metabolism of PAXENE is catalyzed by cytochrome P450 iso-enzymes CYP3A4 and CYP2C8. In the absence of formal clinical drug interaction studies, caution should be exercised when administering PAXENE concomitantly with known substrates or biinhitors of the cytochrome P450 iso-enzymes CYP2C8 and CYP3A4. In recent publications, it was reported that montelukast (Singulair®) is a *potent in vitro* inhibitor of the cytochrome P450 2C8 enzyme and therefore has the potential for drug interactions with substrates of the pathway. Concomitant administration of montelukast has the potential to decrease the metabolic clearance of drugs that are primarily metabolized by CYP 2C8 (or possessing CYP-2C8-catalyzed metabolism as a major clearance pathway) which may result in an increase in plasma concentrations of these drugs and associated risks of dose-related toxicity. (See ACTIONS AND CLINICAL PHARMACOLOGY).

Studies conducted in AIDS-KS patients, who were taking PAXENE and multiple concomitant medications, suggests that the systemic clearance of paclitaxel was significantly lower ($p < 0.05$) in the presence of nelfinavir and ritonavir, but not indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, Paxene should be administered with caution in patients receiving these protease inhibitors as concomitant therapy.

Hematology: PAXENE therapy should not be administered to patients with baseline neutrophil counts of less than 1,000 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving PAXENE. Patients should not be re-treated with subsequent cycles of PAXENE until neutrophils recover to a level >1,000 cells/mm^3 and platelets recover to a level >75,000 cells/mm^3. In the case of severe neutropenia (<500

cells/mm^3 for seven days or more) during a course of PAXENE therapy, a 25% reduction in dose for subsequent courses of therapy is recommended. (See WARNINGS). In the AIDS-KS clinical trial, the majority of patients were administered granulocyte colony stimulating factor (G-CSF).

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with PAXENE. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with 3 hour infusions of PAXENE should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). 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 PAXENE and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with PAXENE.

Cardiovascular: Hypotension, hypertension, bradycardia, tachycardia and T-wave abnormalities have been observed during administration of PAXENE, but generally did not require treatment.

One AIDS-KS patient died of congestive heart failure and pulmonary hypertension, both of which were considered related to PAXENE. Frequent vital sign monitoring, particularly during the first hour of PAXENE infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See WARNINGS section.)

Nervous System: Although the occurrence of peripheral neuropathy is observed with PAXENE, the development of severe symptoms is unusual. With severe peripheral neuropathy due to PAXENE, a dose reduction of 25% for all subsequent courses of PAXENE is recommended.

Hepatic: The liver plays a major role in the metabolism of PAXENE. Studies in patients with advanced AIDS-related KS and impaired hepatic function have not been performed. PAXENE should not be used in patients with documented moderate or severe hepatic impairment. Inadequate data are available to recommend dosage modifications in patients with mild liver impairment. Caution should be exercised when administering PAXENE in combination with other agents that alter hepatic function.

Carcinogenesis, Mutagenesis Impairment of Fertility: The carcinogenic potential of PAXENE has not been studied. Paclitaxel has been shown to be clastogenic *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO gene mutation assay.

Fertility Studies: Studies to investigate the effect of PAXENE on fertility have not been conducted. However, repeat dose studies indicate atrophy of the reproductive tract in male and female rats at doses of 8.5 mg/kg/day for 5 days and irreversible aspermia in dogs at 3 mg/kg/week for 6 weeks (about ½ and 3/5 the daily maximum recommended human dose on a mg/m^2 basis, respectively).

Nursing Mothers: It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving PAXENE.

Pediatric Use: The safety and effectiveness of PAXENE in children have not been established.

Elderly Patients: The safety and effectiveness of PAXENE in elderly patients have not been established.

Renal: Studies in patients with renal impairment have not been performed and there are insufficient data to permit dosage recommendations.

ADVERSE REACTIONS

Data are based on the experience in a phase II, non-comparative study of 107 patients with AIDS-KS at a dose of 100 mg/m^2 PAXENE (paclitaxel) every 2 weeks. Discontinuation of treatment due to toxicity was reported in 3% of all patients or core patients, whereas 12% of all patients and 11% of core patients had dose-reductions. About 5% of treatment cycles in all patients or core patients, were delayed due to toxicity. A total of 160 events were judged severe, 54 were life threatening and 12 were associated with death in the core population. One death in a patient with pancytopenia was reasonably attributed to PAXENE.

The frequency and severity of key adverse events considered possibly or probably related to Paxene are presented in the following table:

SUMMARY OF ADVERSE EVENTS IN PATIENTS RECEIVING 100 mg/m^2 over 3 h Q2W PAXENE	**% Incidence**	
	All patients (n = 107)	Core patients (n=63)
· **Bone Marrow**		
- Neutropenia		
All	90	89
≥grade 3 (<1,000/mm^3)	68	68
Febrile neutropenia	14	14
- Leukopenia		
All	82	81
≥grade 3 (<1,000/mm^3)	50	52
- Thrombocytopenia		
All	50	52
≥grade 3 (<50,000/ mm^3)	9	14
- Anemia		
All	61	62
≥grade 3 (< 8 g/dL)	10	14
· **Hypersensitivity**		
- All	10	11
- Grade 3	<3	0
· **Peripheral Neuropathy**		
- All	26	24
- Severe symptoms (≥grade 3)	2	3
· **Myalgia/Arthralgia**		
- Any symptoms	18	25
- Severe symptoms (≥grade 3)	1	2
· **Gastrointestinal**		
- Vomiting	13	14
- Nausea	26	27
- Diarrhea	22	22
- Mucositis	5	14
· **Alopecia**	62	68
· **Hepatic (Patients with normal baseline and data on study)**		
- Bilirubin elevations		
All	28	33
≥grade 3	12	15
- Alkaline phosphatase elevations		
All	43	50
≥grade 3	1	0
- AST (SGOT) elevations		
All	44	50
≥grade 3	1	2
- ALT (SGPT) elevations		
- AST (SGOT) elevations		
All	37	38
≥grade 3	3	2
· **Injection Site Reaction/Phlebitis**	3	8
· **Discontinuation for drug toxicity**	3	3

** All patients received premedication*

Hematologic: Bone marrow suppression was the major dose limiting toxicity of PAXENE. Neutropenia was the most important hematologic toxicity. During the first course of treatment, severe neutropenia (<500 cells/mm^3) occurred in 20% of KS patients. During the entire treatment period severe neutropenia was reported in 39% of KS patients. Neutropenia was present for more than seven days in 41% of patients and for 30-35 days in 8% of patients. Neutropenia resolved within 35 days in all patients who were followed. The incidence of grade 4 neutropenia lasting 7 days or more was 22%.

Febrile neutropenia occurred in 14% of KS patients. Opportunistic infections occurred in 53% of patients. Upper respiratory tract infections were the most frequently reported infectious complications, but were considered unrelated to PAXENE. There were three septic episodes (2.8%) during PAXENE administration related to drug in the KS study that proved fatal.

During the study, thrombocytopenia occurred in 50% of KS patients who had a normal baseline; it was mild in 41% and severe (<50,000 cells/mm^3) in 9%. A total of 14% of KS patients experienced a drop in their platelet count below 75,000 cells/mm^3 at least once while on treatment. Bleeding episodes related to PAXENE were reported in <3% of KS patients, but the hemorrhagic episodes were localized.

Anemia (Hb<12 g/dL) was observed in 61% of patients, and was severe (Hb <8 g/dL) in 10% of patients. Red cell transfusions were required in 21% of all AIDS-KS patients.

Hypersensitivity Reactions (HSRs): All patients on 3-hour infusions received premedication prior to PAXENE administration (see WARNINGS and PRECAUTIONS, Hypersensitivity Reactions sections). Hypersensitivity reactions during infusion were observed in 10% of KS patients, with 3% of patients experiencing a severe reaction. These reactions consisted mostly of flushing, rash, hypertension, nausea and headache. The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Cardiovascular: Significant cardiovascular events possibly related to PAXENE occurred in <1% of patients and included hypertension and congestive heart failure.

One AIDS-KS patient died of congestive heart failure and pulmonary hypertension, both of which were considered related to PAXENE.

Neurologic: Peripheral neuropathy was observed in 26% (severe in 2%) of patients in the KS study.

Arthralgia/Myalgia: Up to 13% and 18% of AIDS-KS patients

experienced arthralgia and myalgia related to PAXENE, respectively, with 1% having severe symptoms.

Hepatic: Among AIDS-KS patients (where more than half of the patients were on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these tests, the increases were severe in 12%, 1% and 1% of cases, respectively.

Gastrointestinal (GI): Nausea, vomiting and diarrhea were reported in 26%, 13% and 4%, respectively, of AIDS-KS patients. These manifestations were usually of mild to moderate severity.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, reported in 3%, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. A specific treatment for extravasation reactions is unknown at this time.

Other Clinical Events: Alopecia was observed in 62% of AIDS-KS patients. Transient skin changes due to PAXENE have been observed, but no other skin toxicities were significantly associated with PAXENE administration. Rare observations of nail changes (changes in pigmentation or discoloration of nail bed) have been reported.

Two instances of malignancy occurred in AIDS-KS patients receiving PAXENE in the pivotal study. One patient developed CNS lymphoma and one patient developed rectal squamous carcinoma in situ. In addition, one patient developed generalized lymphadenopathy that was not due to AIDS-KS. While it is impossible to definitely ascribe these three events to PAXENE, it is possible that they reflect additional immunosuppression induced by both PAXENE and the frequent use of steroid premedication. The possibility that prolonged treatment with this agent may be associated with an increased risk of malignancy should be considered when treating AIDS-KS patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known antidote for PAXENE (paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized 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 PAXENE (paclitaxel) solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to PAXENE administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before PAXENE, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to PAXENE, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before PAXENE. In patients previously treated with chemotherapy for Kaposi's sarcoma, the recommended regimen is PAXENE 100 mg/m^2 administered intravenously over three hours every two weeks.

Courses of PAXENE should not be repeated until the neutrophil count is at least 1,000 cells/mm^3 and the platelet count is at least 75,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during PAXENE therapy should have dosage reduced by 25% for subsequent courses of PAXENE. Filgrastim (G-CSF), which was administered at any time to 60% of AIDS-KS patients, should be use as recommended in labeling. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: PAXENE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling PAXENE. The use of gloves is recommended. If PAXENE solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PAXENE contacts mucous membranes, the membranes should be flushed thoroughly with water.

Preparation for Intravenous Administration: PAXENE injection must be diluted prior to infusion. PAXENE should be diluted in 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 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 24 hours at ambient temperature (approximately 25ºC) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have

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. PAXENE solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those that are polyethylene-lined, should be used.

PAXENE 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.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

PHARMACEUTICAL INFORMATION

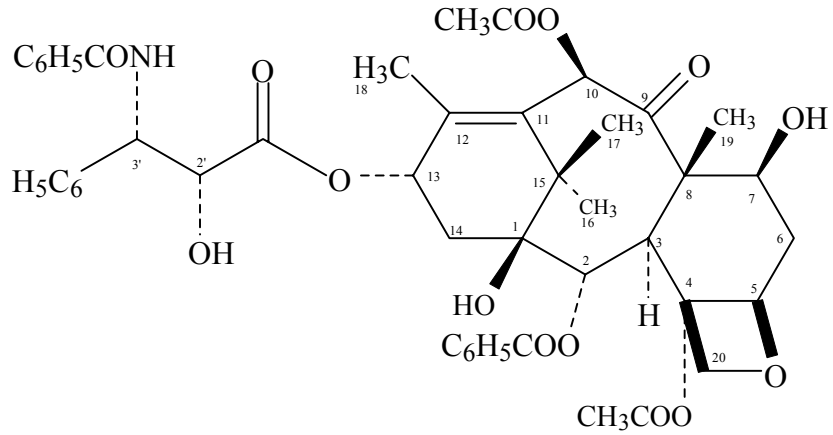
I. DRUG SUBSTANCE

Proper Name: paclitaxel

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

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

Structural formula:



Molecular Weight: 853.9

Description: White to off-white <u>crystalline</u> powder. It is highly lipophilic, insoluble in water, and melts at 213-216ºC.

II. COMPOSITION

Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of polyoxyl 35 castor oil, 2 mg citric acid and 49.7% (v/v) dehydrated alcohol, USP.

III. STABILITY AND STORAGE RECOMMENDATIONS

Paclitaxel Injection should be stored at room temperature (15 - 25º C). Retain in the original package to protect from light. Once punctured, the 5 mL and 25 mL multidose vials of paclitaxel are stable for 28 days at room temperature protected from light.

Solutions for infusion prepared as recommended may be stored at room temperature only if necessary. However, the infusion should be initiated within 24 hours of reconstitution.

IV. PREPARATION FOR INTRAVENOUS ADMINISTRATION

Contact of the undiluted PAXENE (paclitaxel) concentrate with plasticized PVC equipment or devises used to prepare solutions for infusion is not recommended (see DOSAGE AND ADMINISTRATION).

PAXENE (paclitaxel) must be diluted prior to infusion. PAXENE should be diluted in 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 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. Solutions for infusion should be initiated within 24 hours of reconstitution

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 filter).

V. SPECIAL INSTRUCTIONS

PAXENE is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling PAXENE. The use of gloves is recommended. If PAXENE solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PAXENE contacts mucous membranes, the membranes should be flushed thoroughly with water

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all

of the procedures recommended in the guidelines are necessary or appropriate.

Safe Handling References

1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253 (11): 1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.

4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983; 1:426-428.

5. Jones RB, et al: Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept./Oct. 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.

7. Controlling occupational exposure to hazardous drugs (OSHA WORK-PRACTICE GUIDELINES). Am J Health-Syst Pharm 1996; 53:1669-1685.

AVAILABILITY OF DOSAGE FORMS

PAXENE (paclitaxel) is available in 30 mg (5 mL) and 150 mg (25 mL) multiple-dose vials at a concentration of 6 mg/mL.

PHARMACOLOGY

Preclinical Pharmacology

In Vitro

Paclitaxel promotes microtubule assembly and binds to polymerized

tubulin (microtubule) *in vitro* and *in vivo*. This binding of paclitaxel to microtubules is distinct from that of vinblastine, podophyllotoxin, colchicine or guanosine diphosphate (GDP). Moreover, paclitaxel inhibits the elongation of spindles and stabilizes the mitotic spindle microtubules. Cell replication is arrested in the G2/M phase of the cell cycle.

Paclitaxel was active against human cancer cell lines, breast (MCF-7, MDA-MB), neuroblastoma (VA-N-BR2, SK-N-AS), glioblastoma multiforme (VA-MG-SL, U-373-MG) neuroectodermal (SK-N-LO, SK-PN-DW), leukemia, (HL-60), adenocarcinomas (A549, Mca-4, Mca-29, Mca-35, Mc-K, Oca-1, AC-56, HcA-I, PC-Sh, HT-29), saquamous cell carcinoma (SCC-IV, SCC-VII), sarcomas (FSa-II, Sa-IIa, Sa-NH, NFSa, Sa-4I020), and lymphoma (Ly-TH) cervical carcinoma (HeLa), and ovarian carcinoma (OVG-1). The IC_{50} and IC_{90} values of paclitaxel in HL-60 cells after 24 hour exposure were 3 and 10 nM, respectively.

In Vivo

Paclitaxel (i.p.) had antitumor activity of varying degrees against murine leukemias (L1210, P388 and P1534) and good activity against murine solid tumors (B16 melanoma, colon C26, and M109). Paclitaxel in combination with vinorelbine, both administered i.p., has also been shown to be active against P388. IV paclitaxel was also effective against other solid tumors (HCT-116 colon, L2987 lung carcinoma, and LX-1 lung carcinoma, and OCA-1 carcinoma). Paclitaxel (s.c.) was also effective against human xenografts, (CX-1 human colon carcinoma, LOX amyelonic melanoma, and MS-1 breast carcinoma). IV paclitaxel was also active against human xenografts (A2780 ovarian carcinoma, HOC22 and HOC8 ovarian cancer, A431 vulva, H2981 lung carcinoma. The antitumor efficacy depended on the route of implantation of tumor cells and the route of administration of paclitaxel. In several cases, total tumor regressions have been demonstrated.

Paclitaxel was found to inhibit the growth of spindle cells derived from Kaposi's sarcoma at a concentration of approximately 10 nM. In the majority of sensitive cell lines, the concentration of paclitaxel needed to inhibit tumor cell growth by 50% was <2.5 nM, which in most instances was the lowest concentration tested.

Clinical Pharmacology

Pharmacokinetic parameters were also assessed in adult cancer patients in doses varying from 135 to 225 mg/m^2 given over 3 hours. C_{max} and AUC increased disproportionately as the dose increased, indicating the nonlinearity of paclitaxel pharmacokinetics.

Although no formal single-agent drug-interaction studies were conducted, mean clearance values of paclitaxel were similar when obtained during treatment with (20.7 L/h/m^2 , n=7) and without (24.5 L/h/m^2, n=7) indinavir, a protease inhibitor which is a substrate of CYP3A4 (see WARNINGS). In the presence of ritonavir (n=4) and nelfinavir (n=3), mean clearance of paclitaxel fell ($p<0.05$) to 12.3 and 14.1 L/h/m^2, respectively.

TOXICOLOGY

Acute Toxicity

Species and Strain	Formulation and dosage	Time of deaths and period of observations	Significant Results
Rat Sprague-Dawley 8M, 8F	Paclitaxel in Cremophor EL: alcohol diluted with saline at 21.55, 32.53 mg/kg (males) 26.03, 35.66 mg/kg (females) i.p. administration	Daily observations for 29 days. No mortalities noted.	Clinical signs: Prostration and lethargy on day of dosing for vehicle group, lethargy, rough coat, soft feces and hunched posture through day 10 (high dose) and through day 4 (low dose). Severity was dose related. Histological lesions of the gastrointestinal tract were reversible and generally dose-related. Lymphatic system and bone marrow lesions were also reversible. Most paclitaxel-treated rats displayed reproductive tract lesions which were not dose-related.
Rat Sprague-Dawley 10M, 10F	Solutions of Paclitaxel in Cremophor EL: alcohol diluted with saline at 1.0, 3.0, 9.0, 27 and 60 mg/kg i.v. administration	Observations immediately and at 1 and 4 hr post dose and daily for 14 days. No deaths up to 9.0 mg/kg; 9 males and 10 females died within 1 hr in vehicle group; 5 males died at 1 hr and 4 males died on days 2-15 in the 27 mg/kg group; all animals died within 1 hr in the 60 mg/kg group.	Clinical signs: Lethargy, lack of muscle tone, tremors, twitches and spasms immediately after dosing, piloerection, difficulty breathing, prostrate, and lethargy at 1 and 4 hr post dosing in the vehicle, 27 and 60 mg/kg groups. No clinical signs in the 1.0, 3.0 and 9.0 mg/kg groups.
Rat Sprague-Dawley 5M, 5F	Paclitaxel in Cremophor EL: alcohol (50:50) at 35, 50, 70, 90 mg/kg i.v. administration	Observations immediately and 1 and 4 hr post dosing and daily for 21 days. Two vehicle control rats died on the day of dosing, within 4 and 24 hr, one rat in the 95 mg/kg group died on day 10.	Clinical signs: Piloerection, difficulty breathing, prostrate, staggering gait and lethargy at 1 and 4 hr in the vehicle and all paclitaxel groups. Necrosis of the tail, due to vehicle, at the injection site, in vehicle and paclitaxel groups on days 2-22. Piloerection, soft stool, hind leg immobility, hair loss on neck, soiled fur, lethargy in vehicle, 35, 70, 95 groups on days 2-14. Organ weights: Reduced liver weight at 95 mg/kg, reduced testicular weight (not dose-related), increased spleen weight in females at 35 mg/kg.
Dog Beagle 2M, 2F	Paclitaxel in Cremophor EL: alcohol diluted with saline at 1.13, 2.25, 9.0 mg/kg i.v. administration	Daily observations for 58 days. No mortalities noted	Clinical signs: Cutaneous erythema, edema in whole body, head shaking, hypotension, tachycardia, thready pulse, collapse, cool extremities, vasodilatation, hypothermia, shivering and vomiting in vehicle group within 15 min after dosing, all dogs were normal within 6 hr. Depression, pyresis, vomiting and diarrhea on day 2 in high dose group persisting until day 7. Histological lesions: Gastrointestinal tract (mild), bone marrow and of the lymph system (high dose) were reversible. Reversible testicular cell degeneration and necrosis (mid and high dose).

Long-Term Toxicity

Species and Strain	Formulation and dosage	Time of deaths and period of observations	Results
Rat Sprague-Dawley 10M, 10F	Solutions of Paclitaxel in Cremophor EL: alcohol diluted with saline at 1, 3 and 9 mg/kg. Control groups: saline or vehicle. Administered once a day, 5 consecutive days. Conc.: 0.1, 0.3 or 0.9 mg/mL i.v. administration	Observations immediately and at 1 and 4 hr after each dose and daily for 28 days after the last dose. No mortalities in control, 1 and 3 mg/kg groups. 6 males and 6 females died between days 8 and 14 in the 9 mg/kg group	No clinical signs in the control, 1 and 3 mg/kg groups. Piloerection, staggered gait, soft stool, diarrhea, bruised mouth, lethargy between days 5 and 24 in the 9 mg/kg group. Hematological effects: Slight changes in hematocrit, MCV, MCH, MCHC, RBC counts and hemoglobin concentrations usually at the two higher dose levels. Marked effects on platelet, leukocyte and differential leukocyte counts on day 8 (up to 74%, 85% and 80%, respectively). Heart, lung and liver relative weight were increased in males, and the brain weight in females at 9 mg/kg. Increased extramedullary hematopoiesis was observed in the spleen of high dose males.
Rat Crl: CD®BR 10M, 10F	Paclitaxel biomass (*T. hicksii*) or bark (*T. brevifolia*) in Cremophor EL: alcohol diluted with saline at 2.5, 8.5 mg/kg. Control groups: saline or vehicle. Administered once a day, 5 consecutive days. Conc: 2 mg/mL i.v. administration	Observations before dosing and 15 min and 2 h after each dose during the 5-day dosing period, and twice daily for 28 days after the dosing period. Two males died on day 3 in the vehicle control group, 6 males and 5 females died between days 7 and 11 in the high dose paclitaxel biomass group, 7 males and 5 females died between days 5 and 10 in the high dose paclitaxel bark group.	Decreased defecation, soft stool or mucoid stool, yellow stain in anogenital region in high dose groups during the dosing period. Yellow stain in anogenital region in 2 low dose animals during dosing and post dosing periods, anogenital staining, decreased activity, hunched posture, decreased defecation, soft stool, labored breathing, hair loss in high dose groups during post dose period. Leukopenia, neutropenia, lymphopenia, thrombocytopenia and reticulocytopenia were observed in the 8.5 mg/kg animals and to a lesser extent at 2.5 mg/kg/day. Most of these effects were reversible in the lower dose group. Paclitaxel from either source at 8.5 mg/kg/day caused alterations in the bone marrow slides that corresponded to the alterations noted in the peripheral blood hemogram. Macroscopic changes only in the high dose group: ulcerations in the cecum and stomach, enlarged adrenals. The changes observed were comparable for both sources of paclitaxel.
Dog Beagle	Paclitaxel in Cremophor EL:	Observations during dosing and 1 hr after dosing on	Vehicle related signs included flushed skin, increased activity,

4M, 4F in saline control, low and mid dose groups 8M and 8F in other groups Recovery: (4 w): 4/sex/ controls, 4F at 3 mg/kg	alcohol diluted with saline at 0.3, 1.0, 3.0 mg/kg Administered once weekly for 6 weeks Rate: 0.25 mL/min/kg. Conc.: 0.6 mg/mL. i.v. infusion	day of dosing and daily on non-dosing days during the dose period. Daily observations for 28 days of half of the animals in the vehicle and high dose groups after completion of the dosing period. One high dose male died spontaneously 5 days after the first dose; cause of death was not established. No other mortalities were noted.	discolored gums, abnormal vocalization, edema of head, neck and ears and urticaria of head and ears within 20 min after initiation of dosing, signs not evident within 1 hr after initiation of dosing, following disappearance of signs animals displayed decreased activity and vomiting, intensity and duration of signs decreased in each subsequent dosing. No paclitaxel related signs during the recovery period. Hematological findings with paclitaxel at 3.0 mg/kg included mild anemia, moderate leukopenia, neutropenia, lymphopenia in males and reticulocytopenia, which were reversed during the 4-week recovery period. Paclitaxel did not cause any macroscopic pathology findings or organ weight changes. Paclitaxel-related microscopic findings included extramedullary hematopoiesis in males and females, and lymphoid depletion and seminiferous tubule alteration in high-dosed males. The seminiferous tubules remained unchanged during the 4-week recovery period.

Reproductive Toxicity

Species and strain	Formulation and dosage	Period of observations	Results
Rat Sprague-Dawley 25 F	Solutions of Paclitaxel in Cremophor EL:alcohol diluted with saline at 0.3, 0.6, 1.2 mg/kg daily on gestation days 7 to 17. i.v. administration	Observations before and 1 hr after each dose and twice daily till completion on gestation day 20. No mortalities were noted.	Alopecia, bruised tail (days 9, 12), red perivaginal discharge (days 16, 17), chromorhinorrhea (day 20) in 1.2 mg/kg group, decreased maternal body weight gains, body weights, and food consumption in 0.6 and 1.2 mg/kg groups. Early resorptions, resorbed conseptuses, retarded fetal ossification in 0.6 and 1.2 mg/kg groups, increased early and late resorptions, dams with resorptions, resorbed conceptuses, reduced live fetal body weights in 1.2 mg/kg group, increased incidence of cervical rib at 7^{th} cervical vertebra in 1.2 mg/kg group.

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