PACLITERO 30

(Paclitaxel Injection USP 30 mg/5 mL) (6 mg/mL)

1.5. PRODUCT INFORMATION

1.5.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

1.5.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished pharmaceutical product

INN Name: Paclitaxel Injection USP 30 mg/5 mL (6 mg/mL)

Trade Name: PACLITERO 30

Strength: 30 mg/5 mL (6 mg/mL)

Pharmaceutical form: Injection

2. Qualitative and quantitative composition

Each mL contains 6 mg Paclitaxel USP, 527 mg of polyoxyl 35 castor oil (cremophor ELP) USP-NF, 0.497 ml of Dehydrated Alcohol USP and 2 mg Anhydrous Citric acid USP.

3. Pharmaceutical form

Dosage form: Injection

Description: Clear colorless to slightly yellow viscous solution free from visible particles.

4. Clinical particulars

4.1 Therapeutic indications

Paclitaxel Injection, USP is indicated as subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, paclitaxel injection, USP is indicated in combination with cisplatin.

Paclitaxel Injection, USP is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptornegative tumors.

Paclitaxel Injection, USP is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Paclitaxel Injection, USP in combination with cisplatin, is indicated for the first-line treatment of nonsmall cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Paclitaxel Injection, USP is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

4.2 Posology and method of 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 paclitaxel injection, USP 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 paclitaxel injection, USP administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel injection, USP, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to paclitaxel injection, USP, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before paclitaxel injection, USP.

For patients with carcinoma of the ovary the following regimen is recommended:

1) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered

a. Paclitaxel injection, USP administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or

b. Paclitaxel injection, USP administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.

2) In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel injection, USP has been used at several doses and schedules; however, the optimal regimen is not yet clear.

The recommended regimen is paclitaxel injection, USP 135 mg/m2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with carcinoma of the breast, the following is recommended:

1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is paclitaxel injection, USP, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for 4

courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used 4 courses of doxorubicin and cyclophosphamide.

2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel injection, USP at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with non-small cell lung carcinoma, the recommended regimen, given every 3 weeks, is paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with AIDS-related Kaposi's sarcoma, paclitaxel injection, USP administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45 to 50 mg/m2/week). In the 2 clinical trials evaluating these schedules, 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 in patients with advanced HIV disease, the following modifications are recommended in these patients:

1) Reduce the dose of dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead of 20 mg PO);

2) Initiate or repeat treatment with paclitaxel only if the neutrophil count is at least 1,000 cells/mm^3;

3) Reduce the dose of subsequent courses of paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); and

4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast and NSCLC), courses of paclitaxel 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. Paclitaxel should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm3 for a week or longer) or severe peripheral neuropathy during Paclitaxel Injection, USP therapy should have dosage reduced by 20% for subsequent courses of paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: Paclitaxel is a cytotoxic anticancer drug and, as

with other potentially toxic compounds, caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel 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.

Hepatic Impairment: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III to IV myelo suppression. Recommendations for dosage adjustment for the first course of therapy are shown in below table for both 3- and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelo suppression.

Table. Recommendations for Dosing in Patients with Hepatic Impairment Based on Clinical Trial Data[a]

Degree Of Hepatic Impairment			**Recommended paclitaxel Dose[c]**
Transaminase Levels		**Bilirubin Levels[b]**	
24-Hour Infusion			
<2 x ULN	and	≤1.5 mg/dL	135 mg/m^2
2 to <10 x ULN	and	≤1.5 mg/dL	100 mg/m^2
<10 x ULN	and	1.6 - 7.5 mg/dL	50 mg/m^2
≥10 x ULN	or	>7.5 mg/dL	Not Recommended
3-Hour Infusion			
<10 x ULN	and	≤1.25 x ULN	175 mg/m^2
<10 x ULN	and	1.26-2.0 x ULN	135 mg/m^2
<10 x ULN	and	2.01-5.0 x ULN	90 mg/m^2
≥10 x ULN	or	>5.0 x ULN	Not Recommended

[a] these recommendations are based on dosages for patients without hepatic imairement of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for aids-related kaposi's sarcoma).

[b] differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

[c] dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

Preparation and Administration Precautions: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-4]

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel Injection, USP. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness.

If paclitaxel 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.

Preparation for Intravenous Administration: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) 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 I.V. tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl) phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended.

Paclitaxel 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.

Paclitaxel 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.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

Stability: Unopened vials of Paclitaxel Injection, USP are stable until the date indicated on the package when stored between 20° to 25°C (68° to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours.

4.3 Contraindications

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

Paclitaxel Injection, USP should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1,000 cells/mm^3.

4.4 Special warnings and precautions for use

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3 (<1,000

cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 (>1,000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Pregnancy: Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If Paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised 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 Paclitaxel Injection, USP solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel 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: In a Phase I trial using escalating doses of paclitaxel (110 to 200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e., paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 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 paclitaxel. Patients should not be retreated with subsequent cycles of paclitaxel 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/mm3 for seven days or more) during a course of paclitaxel 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, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1,000 cells/mm^3.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Polyoxyl 35 Castor Oil, USP/NF (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel 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 paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Cardiovascular: Hypotension, bradycardia, and hypertension have been observed during administration of Paclitaxel Injection, USP, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When paclitaxel is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Nervous System: Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of paclitaxel.

Paclitaxel Injection, USP contains dehydrated alcohol USP (Ethanol) 0.497 mL; consideration

should be given to possible CNS and other effects of alcohol.

Hepatic: There is limited evidence that the myelotoxicity of Paclitaxel may be exacerbated in patients with serum total bilirubin >2 times ULN. Extreme caution should be exercised when administering Paclitaxel to such patients, with dose reduction as recommended in.

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

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test of the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

Pregnancy: Teratogenic Effects: Pregnancy Category D.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. 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 paclitaxel therapy.

Pediatric Use: The safety and effectiveness of paclitaxel in pediatric patients have not been

established.

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

Geriatric Use: Of 2228 patients who received paclitaxel in 8 clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In 2 clinical studies in NSCLC, the elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group. Below Table presents the incidences of Grade IV neutropenia and severe neuropathy in clinical studies according to age.

Table. Selected adverse events in geriatric patients receiving paclitaxel in clinical studies

INDICATION (Study/Regimen)	Patients (N/Total [%])			
	Neutropenia (Grade IV)		Peripheral Neuropathy (Grades III/IV)	
	Age (y)		Age (y)	
	≥65	<65	≥65	<65
• **OVARIAN Cancer** (Intergroup first-line/ T175/3 c75[a])	34/83 (41)	78/252 (31)	24/84 (29)*[b]	46/255 (18)[b]
(GOG-111 First-Line/ T135/24 C75[A])	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
(Phase 3 second-line/ T175/3[c])	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
(Phase 3 second-line/ T175/24[c])	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
(Phase 3 second-line/ T135/3[c])	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
(Phase 3 second-line/ T135/24[c])	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
(Phase 3 second-line Pooled)	47/82 (57)*	141/319 (44)	1/83 (1)	2/320 (1)
• **adjuvant breast Cancer** (Intergroup/AC followed By T[d])	56/102 (55)	734/1468 (50)	5/102 (5)[e]	46/1468 (3)[e]
• **BREAST Cancer after Failure of Initial Therapy**				
(Phase 3/T175/3[c])	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
(Phase 3/T135/3[c])	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
• **Non-Small Cell LUNG Cancer**				
(Ecog/T135/24 C75[a])	58/71 (82)	86/124 (69)	9/71 (13)[f]	16/124 (13)[f]
(Phase 3/T175/3 C80[a])	37/89 (42)*	56/267 (21)	11/91 (12)*	11/271 (4)

* P<0.05

A paclitaxel dose in mg/m^2/infusion duration in hours; cisplatin doses in mg/m^2.

B peripheral neuropathy was included within the neurotoxicity category in the intergroup first-line ovarian cancer study.

C paclitaxel dose in mg/m^2/infusion duration in hours.

D paclitaxel (t) following 4 courses of doxorubicin and cyclophosphamide (ac) at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

E peripheral neuropathy reported as neurosensory toxicity in the intergroup adjuvant breast cancer study.

F peripheral neuropathy reported as neurosensory toxicity in the ecog nsclc study.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions: In a Phase I trial using escalating doses of paclitaxel (110 to 200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e., paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4.

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Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

4.6 Pregnancy and lactation

Pregnancy: Teratogenic Effects: Pregnancy Category D.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. 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 paclitaxel therapy.

Pediatric Use: The safety and effectiveness of paclitaxel in pediatric patients have not been established.

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

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A paclitaxel dose in mg/m^2/infusion duration in hours; cisplatin doses in mg/m^2.

B peripheral neuropathy was included within the neurotoxicity category in the intergroup first-line ovarian cancer study.

C paclitaxel dose in mg/m^2/infusion duration in hours.

D paclitaxel (t) following 4 courses of doxorubicin and cyclophosphamide (ac) at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

E peripheral neuropathy reported as neurosensory toxicity in the intergroup adjuvant breast cancer study.

F peripheral neuropathy reported as neurosensory toxicity in the ecog nsclc study.

4.7 Fertility, pregnancy and lactation

Please refer to 4.6.

4.8 Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that the medicinal product contains alcohol.

The ability to drive or to use machines may be decreased due to alcohol content of this medicinal product.

4.9 Undesirable Effects

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies: Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent Paclitaxel Injection, USP. Two hundred and seventy-five patients were treated in eight Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m2 administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support).

Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m^2) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six patients with breast carcinoma received paclitaxel (135 or 175 mg/m^2) administered over 3 hours in a controlled study.

Table. Summary[a] of Adverse Events in Patients with Solid Tumors Receiving Single-Agent Paclitaxel

	Percent of Patients (N=812)
• **Bone Marrow**	
- Neutropenia <2,000/mm^3	90
<500/mm^3	52
- Leukopenia <4,000/mm^3	90
<1,000/mm^3	17
- Thrombocytopenia <100,000/mm^3	20
	7
	78
	16
• **Hypersensitivity Reaction**[b]	
- ALL	41
- Severe[†]	2
• **Cardiovascular**	
- Vital Sign Changes[c]	
- Bradycardia (N=537)	3
- Hypotension (N=532)	12
- Significant Cardiovascular Events	1
• **Abnormal ECG**	
- All Pts	23
- Pts With Normal Baseline (N=559)	14
• **Peripheral Neuropathy**	
- Any Symptoms	60
- Severe Symptoms[†]	3
• **Myalgia/Arthralgia**	
- Any Symptoms	60
- Severe Symptoms[†]	8
• **Gastrointestinal**	
- Nausea And Vomiting	52
- Diarrhea	38
- Mucositis	31
	Percent 0f Patients (N=812)
• **Alopecia**	87

• Hepatic (Pts with normal baseline and on study data)	
- Bilirubin Elevations (N=765)	7
- Alkaline Phosphatase Elevations (N=575)	22
- AST (SGOT) Elevations (N=591)	19
• Injection Site Reaction	13

[A] Based on worst course analysis.
[B] All patients received premedication.
[C] During the first 3 hours of infusion.
[†] Severe events are defined as at least grade iii toxicity.

None of the observed toxicities were clearly influenced by age.

Disease-Specific Adverse Event Experiences

First-Line Ovary in Combination: For the 1084 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy studies, below table shows the incidence of important adverse events. For both studies, the analysis of safety was based on all courses of therapy (6 courses for the GOG-111 study and up to 9 courses for the Intergroup study).

Table. Frequency[a] of Important Adverse Events in the Phase 3 First-Line Ovarian Carcinoma Studies

	Percent of Patients			
	Intergroup		**GOG-111**	
	T175/3[b] c75[c] (N=339)	**C750[c] C75[c] (N=336)**	**T135/24[b] C75[c] (N=196)**	**C750[c] C75[c] (N=213)**
• Bone Marrow				
- Neutropenia <2,000/mm^3	91[d]	95[d]	96	92
<500/mm^3	33[d]	43[d]	81[d]	58[d]
- Thrombocytopenia				
<100,000/mm^{3e}	21[d]	33[d]	26	30
<50,000/mm^3				
- Anemia <11 g/dLf	3[d]	7[d]	10	9
<8 g/dL	96	97	88	86
- Infections	3[d]	8[d]	13	9
-Febrile	25	27	21	15

Neutropenia	4	7	15[D]	4[D]
• **Hypersensitivity Reaction**				
- All	11[d]	6[d]	8[d,g]	1[d,g]
- Severe[†]	1	1	3[d,g]	–[d,g]
• **Neurotoxicity[h]**				
- Any Symptoms	87[d]	52[d]	25	20
- Severe Symptoms[†]	21[d]	2[d]	3[d]	–[d]
• **Nausea And Vomiting**				
- Any Symptoms	88	93	65	69
- Severe Symptoms[†]	18	24	10	11
	Percent of Patients			
	Intergroup		**GOG-111**	
	T175/3[b] c75[c] (N=339)	**C750[c] C75[c] (N=336)**	**T135/24[b] C75[c] (N=196)**	**C750[c] C75[c] (N=213)**
• **Myalgia/Arthralgia**				
- Any Symptoms	60[d]	27[d]	9[d]	2[d]
- Severe Symptoms[†]	6[d]	1[d]	1	–
• **Diarrhea**				
- Any Symptoms	37[d]	29[d]	16[d]	8[d]
- Severe Symptoms[†]	2	3	4	1
• **Asthenia**				
- Any Symptoms	NC	NC	17[d]	10[d]
- Severe Symptoms[†]	NC	NC	1	1
• **Alopecia**				
- Any Symptoms	96[d]	89[d]	55[d]	37[d]
- Severe Symptoms[†]	51[d]	21[d]	6	8

[a] based on worst course analysis.

[b] paclitaxel (T) dose in mg/m^2/infusion duration in hours.

[c] cyclophosphamide (C) or cisplatin (C) dose in mg/m^2.

[d] p<0.05 by fisher exact test.

[e] <130,000/mm3 in the intergroup study.

[f] <12 g/dl in the intergroup study.

[g] all patients received premedication.

Second-Line Ovary: For the 403 patients who received single-agent Paclitaxel Injection, USP in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

Table. Frequency[a] of Important Adverse Events in the Phase 3 Second-Line Ovarian Carcinoma Study

	Percent of Patients			
	175/3[b] (N=95)	**175/24[b] (N=105)**	**135/3[b] (N=98)**	**135/24[b] (N=105)**
• Bone Marrow				
-Neutropenia				
<2,000/mm^3	78	98	78	98
<500/mm^3	27	75	14	67
-Thrombocytopenia				
<100,000/mm^3	4	18	8	6
<50,000/mm^3	1	7	2	1
-Anemia				
<11 g/dL	84	90	68	88
<8 g/dL	11	12	6	10
-Infections	26	29	20	18
	Percent of Patients			
	175/3[b] (N=95)	**175/24[b] (N=105)**	**135/3[b] (N=98)**	**135/24[b] (N=105)**
•hypersensitivity reaction[c]				
- All	41	45	38	45
- SEVERE[†]	2	0	2	1
• Peripheral Neuropathy				

- Any Symptoms	63	60	55	42
- severe symptoms[†]	1	2	0	0
• **Mucositis**				
- Any Symptoms	17	35	21	25
- Severe Symptoms[†]	0	3	0	2

[a] based on worst course analysis.

[b] paclitaxel dose in mg/m^2/infusion duration in hours

[c] all patients received premedication.

[†] severe events are defined as at least grade iii toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

Adjuvant Breast: For the Phase 3 adjuvant breast carcinoma study, the following table shows the incidence of important severe adverse events for the 3121 patients (total population) who were evaluable for safety as well as for a group of 325 patients (early population) who, per the study protocol, were monitored more intensively than other patients.

Table. Frequencya of Important Severeb Adverse Events in the Phase 3 Adjuvant Breast Carcinoma Study

	Percent of Patients			
	Early Population		**Total Population**	
	AC[C] (n=166)	**AC[C] followed by T[d] (n=159)**	**AC[C] (n=1551)**	**AC[C] followed BY T[d] (n=1570)**
• **Bone Marrow[e]**				
- Neutropenia <500/mm^3	79	76	48	50
- Thrombocytopenia <50,000/mm^3	27	25	11	11
- Anemia <8 g/dL	17	21	8	8
- Infections	6	14	5	6
- Fever Without Infection	–	3	<1	1
• **Hypersensitivity Reaction[f]**	1	4	1	2

• **Cardiovascular Events**	1	2	1	2
• **Neuromotor Toxicity**	1	1	<1	1
• **Neurosensory Toxicity**	–	3	<1	3
• **Myalgia/Arthralgia**	–	2	<1	2
• **Nausea/Vomiting**	13	18	8	9
• **Mucositis**	13	4	6	5

[a] Based on worst course analysis.

[b] Severe events are defined as at least grade iii toxicity.

[c] Patients received 600 mg/m^2 cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m^2, 75 mg/m^2, or 90 mg/m^2 (with prophylactic g-csf support and ciprofloxacin), every 3 weeks for 4 courses.

[d] paclitaxel (T) following 4 courses of ac at a dose of 175 mg/m^2/3 hours every 3 weeks for 4 courses.

[e] the incidence of febrile neutropenia was not reported in this study.

[f] All patients were to receive premedication.

The incidence of an adverse event for the total population likely represents an underestimation of the actual incidence given that safety data were collected differently based on enrollment cohort. However, since safety data were collected consistently across regimens, the safety of the sequential addition of paclitaxel following AC therapy may be compared with AC therapy alone. Compared to patients who received AC alone, patients who received AC followed by paclitaxel experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional 4 courses of treatment with paclitaxel, 2 deaths (0.1%) were attributed to treatment. During paclitaxel treatment, Grade IV neutropenia was reported for 15% of patients, Grade II/III neurosensory toxicity for 15%, Grade II/III myalgias for 23%, and alopecia for 46%.

The incidences of severe hematologic toxicities, infections, mucositis, and cardiovascular events increased with higher doses of doxorubicin.

Breast Cancer After Failure of Initial Chemotherapy: For the 458 patients who received single-agent paclitaxel in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a 3-hour infusion).

Table. Frequency[a] of Important Adverse Events in the Phase 3 Study of Breast Cancer after Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Chemotherapy

		Percent of Patients	
		175/3[B] (N=229)	**135/3[B] (N=229)**
• **Bone Marrow**			
- Neutropenia	<2,000/mm^3	90	81
	<500/ mm^3	28	19
- Thrombocytopenia	<100,000/mm^3	11	7
	<50,000/mm^3	3	2
- Anemia	<11g/dL	55	47
	<8 g/dL	4	2
- Infections		23	15
- Febrile Neutropenia		2	2
• **Hypersensitivity Reaction[c]**			
- All		36	31
- Severe[†]		0	<1
		Percent of Patients	
		175/3[b] (N=229)	**135/3[b] (N=229)**
• **Peripheral Neuropathy**			
- Any Symptoms		70	46
- Severe Symptoms[†]		7	3
• **Mucositis**			
- Any Symptoms		23	17
- Severe Symptoms[†]		3	<1

[a] Based on worst course analysis.
[b] Paclitaxel dose in mg/m^2/infusion duration in hours.
[c] All patients received premedication.
[†] Severe events are defined as at least grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m^2.

First-Line NSCLC in Combination: In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either paclitaxel (T) 135 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2, paclitaxel (T) 250 mg/m^2 as a 24-hour infusion in combination with cisplatin (c) 75 mg/m^2 with G-CSF support, or cisplatin (c) 75 mg/m^2 on day 1, followed by etoposide (VP) 100 mg/m^2 on days 1, 2, and 3 (control).

The following table shows the incidence of important adverse events.

Table. Frequency[a] of Important Adverse Events in the Phase 3 Study for First-Line NSCLC

	Percent of Patients		
	T135/24[b] c75 (n=195)	**T250/24[c] c75 (n=197)**	**VP100[d] c75 (n=196)**
• **Bone Marrow**			
- Neutropenia <2000/mm^3	89	86	84
<500/ mm^3	74[e]	65	55
- Thrombocytopenia <normal	48	68	62
<50,000/mm^3	6	12	16
- anemia <normal	94	96	95
<8 g/dL	22	19	28
- Infections	38	31	35
• **Hypersensitivity Reaction[f]**	16	27	13
- All	1	4[e]	1
- Severe[†]			
• **Arthralgia/Myalgia**	21[e]	42[e]	9
- Any Symptoms	3	11	1
- Severe Symptoms[†]			
• **Nausea/Vomiting**	85	87	81
- Any Symptoms	27	29	22
- Severe Symptoms[†]			
	Percent of Patients		
	T135/24[b] c75 (n=195)	**T250/24[c] c75 (n=197)**	**VP100[d] c75 (n=196)**
• **Mucositis**	18	28	16
- Any Symptoms	1	4	2
- Severe Symptoms[†]			
• **Neuromotor Toxicity**			
- Any Symptoms	37	47	44
- Severe Symptoms[†]	6	12	7
• **Neurosensory Toxicity**	48	61	25
- Any Symptoms	13	28[E]	8
- Severe Symptoms[†]			

• **Cardiovascular Events**			
- Any Symptoms	33	39	24
- Severe Symptoms[†]	13	12	8

[a] Based on worst course analysis.
[b] Paclitaxel (T) dose in mg/m^2/infusion duration in hours; cisplatin (c) dose in mg/m^2.
[c] Paclitaxel dose in mg/m^2/infusion duration in hours with G-CSF support; cisplatin dose in mg/m^2.
[d] Etoposide (VP) dose in mg/m^2 was administered iv on days 1, 2, and 3; cisplatin dose in mg/m^2.
[e] $p<0.05$.
[f] All patients received premedication.
[†] Severe events are defined as at least grade III toxicity.

Toxicity was generally more severe in the high-dose paclitaxel treatment arm (T250/c75) than in the low-dose paclitaxel arm (T135/c75). Compared to the cisplatin/etoposide arm, patients in the low-dose paclitaxel arm experienced more arthralgia/myalgia of any grade and more severe neutropenia. The incidence of febrile neutropenia was not reported in this study.

Kaposi's Sarcoma: The following table shows the frequency of important adverse events in the 85 patients with KS treated with 2 different single-agent paclitaxel regimens.

Table. Frequency[a] of Important Adverse Events in the Aids-Related Kaposi's Sarcoma Studies

	Percent of Patients	
	Study CA139-174 Paclitaxel 135/3[b] q 3 wk	**Study CA139-281 Paclitaxel 100/3[b] q 2 wk**
• **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
	Percent of Patients	
	Study CA139-174 Paclitaxel 135/3[b] q 3 wk (n=29)	**Study CA139-281 Paclitaxel 100/3[b] q 2 wk (n=56)**
• **Opportunistic Infection**		

-Any - Cytomegalovirus - Herpes Simplex - *Pneumocystis Carinii* - *m. avinum intracellulare* - Candidiasis, Esophageal - Cryptosporidiosis - Cryptococcal Meningitis - Leukoencephalopathy	 76 45 38 14 24 7 7 3 –	 54 27 11 21 4 9 7 2 2
• **Hypersensitivity Reaction**[c] - All	14	9
• **Cardiovascular** - Hypotension - Bradycardia	17 3	9 –
• **Peripheral Neuropathy** - Any - Severe[†]	79 10	46 2
• **Myalgia/Arthralgia** - Any - Severe[†]	 93 14	 48 16
• **Gastrointestinal** - Nausea And Vomiting - Diarrhea - Mucositis	69 90 45	70 73 20
• **Renal (Creatinine Elevation)** - Any - Severe[†]	34 7	18 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.
[†] Severe events are defined as at least grade iii toxicity.

As demonstrated in this table, toxicity was more pronounced in the study utilizing paclitaxel at a dose of 135 mg/m2 every 3 weeks than in the study utilizing palcitaxel at a dose of 100 mg/m2

every 2 weeks. Notably, severe neutropenia (76% vs 35%), febrile neutropenia (55% vs 9%), and opportunistic infections (76% vs 54%) were more common with the former dose and schedule. The differences between the 2 studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

Adverse Event Experiences by Body System:

The following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in 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 and that occurred with a difference that was clinically significant in these populations are also described.

The frequency and severity of important adverse events for the Phase 3 ovarian carcinoma, breast carcinoma, NSCLC, and the Phase 2 Kaposi's sarcoma carcinoma studies are presented above in tabular form by treatment arm. 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 patients receiving paclitaxel for the treatment of ovarian, breast, or 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. 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. Elevated liver function tests and renal toxicity have a higher incidence in KS patients as compared to patients with solid tumors.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm3 in 14% of the patients treated with a dose of 135 mg/m^2 compared to 27% at a dose of 175 mg/m^2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose.

Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

In the study where paclitaxel was administered to patients with ovarian carcinoma at a dose of 135 mg/m2/24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the paclitaxel plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the paclitaxel plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the paclitaxel/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When paclitaxel followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (paclitaxel 135 mg/m2/24 hours followed by cisplatin) and 65% (paclitaxel 250 mg/m2/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

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% and 26% of the patients treated with a dose of 135 mg/m^2 or 175 mg/m^2 given as a 3-hour infusion respectively. 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.

Thrombocytopenia was reported. Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/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 Injection, USP dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no 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 (HSRs): All patients received premedication prior to paclitaxel. The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSRs 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. Abdominal pain, pain in the extremities, diaphoresis, and hypertension were also noted.

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. Chills, shock, and back pain in association with hypersensitivity reactions have been reported.

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 3 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/m2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement. Among patients with NSCLC treated with paclitaxel in combination with cisplatin in

the Phase 3 study, significant cardiovascular events occurred in 12 to 13%. This apparent increase in cardiovascular events is possibly due to an increase in cardiovascular risk factors in 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 ECGs at baseline, prior therapy with anthracyclines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported. Congestive heart failure, including cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure, has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Atrial fibrillation and supraventricular tachycardia have been reported.

Respiratory: Interstitial pneumonia, lung fibrosis, and pulmonary embolism have been reported. Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Pleural effusion and respiratory failure have been reported.

Neurologic: The assessment of neurologic toxicity was conducted differently among the studies as evident from the data reported in each individual study. Moreover, the frequency and severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agency 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. Paresthesia commonly occurs in the form of hyperesthesia. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34% to 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. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

In the Intergroup first-line ovarian carcinoma study, neurotoxicity included reports of neuromotor and neurosensory events. The regimen with paclitaxel 175 mg/m^2 given by 3-hour infusion plus cisplatin 75 mg/m^2 resulted in greater incidence and severity of neurotoxicity than the regimen containing cyclophosphamide and cisplatin, 87% (21% severe) versus 52% (2% severe), respectively. The duration of grade III or IV neurotoxicity cannot be determined with precision for the Intergroup study since the resolution dates of adverse events were not collected in the case report forms for this trial and complete follow-up documentation was available only in a minority of these patients. In the GOG first-line ovarian carcinoma study, neurotoxicity was reported as peripheral neuropathy. The regimen with paclitaxel 135 mg/m2 given by 24-hour infusion plus cisplatin 75 mg/m^2 resulted in an incidence of neurotoxicity that was similar to the regimen containing cyclophosphamide plus cisplatin, 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in the Intergroup and GOG trials suggests that when paclitaxel is given in combination 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 a greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent paclitaxel. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving paclitaxel 135 mg/m^2 by 24-hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide.

Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Autonomic neuropathy resulting in paralytic ileus have been reported. Optic nerve and/or visual disturbances (scintillating scotomata) 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 also been received. Convulsions, dizziness, and headache have been reported.

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 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.

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. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.

Hepatic necrosis and hepatic encephalopathy leading to death have reported.

Renal: Among the patients treated for Kaposi's sarcoma with paclitaxel, 5 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 4 patients had renal insufficiency with reversible elevations of serum creatinine.

Patients with gynecological cancers treated with paclitaxel and cisplatin may have an increased risk of renal failure with the combination therapy of paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

Gastrointestinal (GI): 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 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 43 patients with Kaposi's sarcoma complained of diarrhea prior to study start.

In the first-line Phase 3 ovarian carcinoma studies, 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 addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no difference for severe diarrhea in these studies.

Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been reported. 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 Reaction: Injection site reactions, including reactions secondary to extravasation,

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

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

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

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to Paclitaxel -related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. In postmarketing experience, diffuse edema, thickening, and sclerosing of the skin have been reported following paclitaxel administration. Paclitaxel has been reported to exacerbate signs and symptoms of scleroderma.

Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety. In the Phase 3 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.

Conjunctivitis, increased lacrimation, anorexia, confusional state, photopsia, visual floaters, vertigo, and increase in blood creatinine have been reported.

Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and

redness.

4.10 Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Paclitaxel is a novel antimicrotubule agent that 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. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner. 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.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

Table. Summary of Pharmacokinetic Parameters – Mean Values

dose (mg/m_2)	**Infusion Duration (h)**	**N (Patients)**	**C_{max} (ng/mL)**	**AUC $_{(0-\infty)}$ (ng•h/mL)**	**T-HALF (h)**	**CL_T ($L/h/m^2$)**
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C_{max} = Maximum plasma concentration
AUC $_{(0-\infty)}$= area under the plasma concentration-time curve from time 0 to infinity
CL_t = total body clearance

It appeared that with the 24-hour infusion of paclitaxel, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{max} by 87%, whereas the AUC (0-∞) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC (0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of paclitaxel, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m^2 given by 1-hour infusions (n=15), 30 to 275 mg/m^2 given by 6-hour infusions (n=36), and 200 to 275 mg/m2 given by 24-hour infusions (n=54) in Phase 1 & 2 studies. Values for CLT and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of paclitaxel in patients with AIDS-related Kaposi's sarcoma have not been studied.

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

After intravenous administration of 15 to 275 mg/m^2 doses of Paclitaxel injection, USP as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m2 dose of radiolabeled paclitaxel as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. 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. 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-dihydroxy-paclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α- ethinyl estradiol, retinoic acid, 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.

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤2 times upper limit of normal (ULN) administered 175 mg/m2 was increased, but with no apparent increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m2), but no observed increase in plasma exposure. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated. Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test of the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Cremophor ELP USP/NF, Anhydrous Citric acid USP and Dehydrated alcohol USP (Ethanol)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store below 30° C and protect from moisture.

6.5 Nature and contents of container

Glass Vials: 10's count (5 ml glass vial, 20 mm rubber stopper with 20 mm flip of seal)

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Name: **Hetero Labs Limited**

Business Address: 7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar,
Hyderabad-500 018
Andhra Pradesh.

Country: INDIA

8. Manufacture

Holder Name	**:** Hetero Labs Limited
Manufacturing facility	: Hetero Labs Limited (Unit-VI)
Address	: APIIC Formulation SEZ, Survey No. 410 & 411, Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Andhra Pradesh.
Country	: India
Telephone	: 91-08542-202350
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9. Date of revision of the text

May, 2014

PACLITERO 30
(Paclitaxel Injection USP 30mg/5mL) (6mg/mL)

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

1. NAME OF THE FPP

PACLITERO 30 (Paclitaxel Injection USP 30 mg/5ml)

2. METHOD OF ADMINISTRATION

Intravenous use

3. A list of API(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.

Each mL contains 6 mg Paclitaxel USP.

4. List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol, or tartrazine.

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5. Indication(s) and recommended dosage, where practicable

Anti neoplastic drug, 30 mg.

6. The batch number assigned by the manufacturer.

< Batch > <Lot> <BN> {number}

7. The manufacturing and expiry dates in an uncoded form.

MFG: MM/YYYY

EXP: MM/YYYY