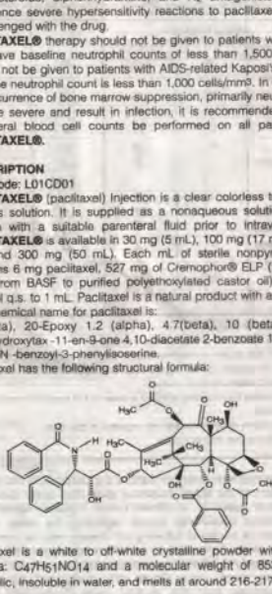
PANATAXEL®
PACLITAXEL

Solution for Injection
Concentrate for Infusion

Prescription Only
Made in Argentina

WARNING
PANATAXEL® (paclitaxel) Injection 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. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 - 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.
PANATAXEL® therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1,000 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 **PANATAXEL®.**

DESCRIPTION
ATC Code: L01CD01
PANATAXEL® (paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. **PANATAXEL®** is available in 30 mg (5 mL), 100 mg (17 mL), 150 mg (25 mL) and 300 mg (50 mL). Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor® ELP (registered trade mark from BASF to purified polyethoxylated castor oil) and absolute ethanol q.s. to 1 mL. Paclitaxel is a natural product with antitumor activity.
The chemical name for paclitaxel is:
5 (beta), 20-Epoxy 1,2 (alpha), 4,7(beta), 10 (beta), 13 (alpha)-hexahydroxytax -11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2 R ,3 S)- N -benzoyl-3-phenylisoserine.
Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula: $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217°C.

CLINICAL PHARMACOLOGY
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, 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. Pharmacokinetic parameters of paclitaxel following 3- and 24-hour infusion 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 1: SUMMARY OF PHARMACOKINETIC PARAMETERS - MEAN VALUES

Dose (mg/m^2)	Infusion duration (h)	N (patients)	C_{max} (ng/mL)	AUC (0-infinity) (ng·h/mL)	T-HALF (h)	CL T (L/h/m^2)
135	24	2	195	6,300	52.7	21.7
175	24	4	365	7,993	15.7	23.8
135	3	7	2,170	7,952	13.1	17.7
175	3	5	3,650	15,007	20.2	12.2

C_{max} = Maximum plasma concentration
AUC (0-Infinity) = 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-infinity) remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C_{max} and AUC (0-infinity) 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 15-135 mg/m^2 given by 1-hour infusions (n=15), 30-275 mg/m^2 given by 6-hour infusions (n=36), and 200-275 mg/m^2 given by 24-hour infusions (n=54) in Phase 1 & 2 studies. Values for CL T 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 µg/mL, indicate that between 89%-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.
After intravenous administration of 15-275 mg/m^2 doses of paclitaxel 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/m^2 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 6 (alpha)-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 (alpha)-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'- p - hydroxypaclitaxel and 6(alpha), 3'- p -dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6(alpha)-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, 17(alpha)-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6(alpha)-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 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.

INDICATIONS AND USAGE
PANATAXEL® is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, **PANATAXEL®** is indicated in combination with cisplatin.
PANATAXEL® 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 receptor-negative tumors.
PANATAXEL® 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.
PANATAXEL®, in combination with cisplatin, is indicated for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
PANATAXEL® is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma (KS).

CONTRAINDICATIONS
PANATAXEL® is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor ELP (polyethoxylated castor oil).
PANATAXEL® should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1,000 cells/mm^3.

WARNINGS
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%-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. **PANATAXEL®** 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 **PANATAXEL®** treatment. Patients should not be retreated with subsequent cycles of **PANATAXEL®** 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 **PANATAXEL®** infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with **PANATAXEL®**.
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 3.0 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 1.0 mg/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 **PANATAXEL®** 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 solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.
PANATAXEL® 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 1 trial using escalating doses of paclitaxel (110-200 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, inhibitors and inducers of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials. 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
PANATAXEL® 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 **PANATAXEL®**. Patients should not be retreated with subsequent cycles of **PANATAXEL®** until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of **PANATAXEL®** 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, **PANATAXEL®**, 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 Cremophor® ELP (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 **PANATAXEL®** 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, 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 **PANATAXEL®** infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When **PANATAXEL®** 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 contains absolute ethanol, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol.
Hepatic
There is limited evidence that the extreme myelotoxicity of paclitaxel may be exacerbate in patients with elevated liver enzymes. Extreme caution should be exercised when administering **PANATAXEL®** to patients with moderate to severe hepatic impairment and dose adjustments should be considered.
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 or 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.

PREGNANCY
Pregnancy "Category D".

NURSING MOTHERS
It is not known whether the drug is excreted in human milk. Following intravenous administration of ^{14}C 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 **PANATAXEL®** 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 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.

ADVERSE REACTIONS

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. Two hundred and seventyfive 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/m²) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirtysix patients with breast carcinoma received paclitaxel (135 or 175 mg/m²) administered over 3 hours in a controlled study.

TABLE 2: SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT PACLITAXEL

	Percent of patients (n=812)
• **Bone marrow**	
- Neutropenia	
< 2,000/mm³	90
< 500/mm³	52
- Leukopenia	
< 4,000/mm³	90
< 1,000/mm³	17
- Thrombocytopenia	
< 100,000/mm³	20
< 50,000/mm³	7
- Anemia (Hb)	
< 11 g/dL	78
< 8 g/dL	16
- Infections	30
- Bleeding	14
- Red cell transfusions	25
- Platelet transfusions	2
• **Hypersensitivity reactions [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
• **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 1,084 patients who were evaluable for safety in the Phase 3 first-line ovary combination therapy studies, table 3 shows the incidence of important adverse events. For both studies, the analysis of safety was based on all courses of therapy (six courses for the GOG-111 study and up to nine courses for the Intergroup study).

TABLE 3: FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 FIRST-LINE OVARIAN CARCINOMA STUDIES

	Percent of patients			
	Intergroup		GOG-111	
	P175/3 [b] c75 [c] (n=339)	C750 [c] c75 [c] (n=336)	P135/24 [b] c75 [c] (n=196)	C750 [c] c75 [c] (n=213)
• **Bone marrow**				
- Neutropenia				
< 2,000/mm³	91 [d]	95 [d]	96	92
< 500/mm³	33 [d]	43 [d]	81 [d]	58 [d]
- Thrombocytopenia				
< 100,000/mm³ [e]	21 [d]	33 [d]	26	30
< 50,000/mm³	3 [d]	7 [d]	10	9
- Anemia (Hb)				
< 11 g/dL [f]	96	97	88	86
< 8 g/dL	3 [d]	8 [d]	13	9
- Infections	25	27	21	15
- Febrile neutropenia	4	7	15 [d]	4 [d]
• **Hypersensitivity reactions**				
- 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/vomiting**				
- Any symptoms	88	93	65	69
- Severe symptoms **	18	24	10	11
• **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 (P) dose in mg/m² /infusion duration in hours. / [c] Cyclophosphamide (C) or cisplatin (c) dose in mg/m². / [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. / [h] In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms. / ** Severe events are defined as at least Grade III toxicity. / **NC** Not Collected.

Second-line ovary

For the 403 patients who received single-agent paclitaxel in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

TABLE 4: FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 SECOND-LINE OVARIAN CARCINOMA STUDY

	Percent of patients (n=612)			
	175/3 [b] (n=95)	175/24 [b] (n=105)	135/3 [b] (n=99)	135/24 [b] (n=105)
• **Bone marrow**				
- Neutropenia				
< 2,000/mm³	78	98	78	98
< 500/mm³	27	75	14	67
- Thrombocytopenia				
< 100,000/mm³	4	18	8	6
< 50,000/mm³	1	7	2	1
- Anemia (Hb)				
< 11 g/dL	84	90	68	88
< 8 g/dL	11	12	6	10
- Infections	26	29	20	18
• **Hypersensitivity reactions [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/m² /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 3,121 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 5: FREQUENCY[a] OF SEVERE[b] 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 P [d] (n=159)	AC [c] (n=1551)	AC [c] followed by P [d] (n=1570)
• **Bone marrow** [e]				
- Neutropenia				
< 500/mm³	79	76	48	50
- Thrombocytopenia				
< 50,000/mm³	27	25	11	11
- Anemia (Hb)				
< 8 g/dL	17	21	8	8
- Infections	6	14	5	6
- Fever without infection	–	3	<1	1
• **Hypersensitivity reactions [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/m² cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m², 75 mg/m², or 90 mg/m² (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for four courses.
[d] Paclitaxel (P) following four courses of AC at a dose of 175 mg/m² /3 hours every 3 weeks for four 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 four courses of treatment with paclitaxel, two 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 6: FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 OF BREAST CANCER AFTER FAILURE OF INITIAL CHEMOTHERAPY OF WITHIN 6 MONTHS OF ADJUVANT CHEMOTHERAPY

	Percent of patients	
	175/3 [b] (n=229)	135/3 [b] (n=229)
• **Bone marrow**		
- Neutropenia		
< 2,000/mm³	90	81
< 500/mm³	28	19
- Thrombocytopenia		
< 100,000/mm³	11	7
< 50,000/mm³	3	2
- Anemia (Hb)		
< 11 g/dL	55	47
< 8 g/dL	4	2
- Infections	23	15
- Febrile Neutropenia	2	2
• **Hypersensitivity reactions [c]**		
- All	36	31
- Severe **	0	<1
• **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/m² /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/m².

First-line NSCLC in combination

In the study conducted by the Eastern Cooperative Oncology Group (ECOG), patients were randomized to either paclitaxel (P) 135 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m², paclitaxel (P) 250 mg/m² as a 24-hour infusion in combination with cisplatin (c) 75 mg/m² with G-CSF support, or cisplatin (c) 75 mg/m² on day 1, followed by etoposide (VP) 100 mg/m² on days 1, 2 and 3 (control).

The following table shows the incidence of important adverse events.

TABLE 7: FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE PHASE 3 STUDY FOR FIRST-LINE NSCLC

	Percent of patients		
	P135/24 [b] c75 (n=195)	P250/24 [c] c75 (n=197)	VP100 [d] c75 (n=196)
• **Bone marrow**			
- Neutropenia			
< 2,000/mm³	89	86	84
< 500/mm³	74 [e]	65	55
- Thrombocytopenia			
< normal	48	68	62
< 50,000/mm³	6	12	16
- Anemia (Hb)			
< normal	94	96	95
< 8 g/dL	22	19	28
- Infections	38	31	35
• **Hypersensitivity reactions [f]**			
- All	16	27	13
- Severe **	1	4 [e]	1
• **Arthralgia/myalgia**			
- Any symptoms	21 [e]	42 [e]	9
- Severe symptoms **	3	11	1
• **Nausea/vomiting**			
- Any symptoms	85	87	81
- Severe symptoms **	27	29	22
• **Mucositis**			
- Any symptoms	18	28	16
- Severe symptoms **	1	4	2
• **Neuromotor toxicity**			
- Any symptoms	37	47	44
- Severe symptoms **	6	12	7
• **Neurosensory toxicity**			
- Any symptoms	48	61	25
- Severe symptoms **	13	28 [e]	8
• **Cardiovascular events**			
- Any symptoms	33	39	24
- Severe symptoms **	13	12	8

[a] Based on worst course analysis.

b Paclitaxel (P) dose in mg/m²/infusion duration in hours; cisplatin (c) dose in mg/m²
c Paclitaxel (P) dose in mg/m²/infusion duration in hours with G-CSF support; cisplatin dose in mg/m².
d Etoposide (VP) dose in mg/m² was administered I.V. on days 1, 2 and 3; cisplatin dose in mg/m².
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 injection treatment arm (P250/c75) than in the low-dose paclitaxel arm (P135/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 two different single-agent paclitaxel

TABLE 8: FREQUENCY[a] OF IMPORTANT ADVERSE EVENTS IN THE AIDS-RELATED KAPOSI'S SARCOMA STUDIES

	Percent of patients	
	Paclitaxel 135/3 [b] q 3wk (n=29)	Paclitaxel 100/3 [b] q 2wk (n=56)
• Bone marrow		
- Neutropenia		
< 2,000/mm³	100	96
< 500/mm³	76	36
- Thrombocytopenia		
< 100,000/mm³	52	27
< 50,000/mm³	17	5
- Anemia (Hb)		
< 11 g/dL	86	73
< 8 g/dL	34	25
- Febrile neutropenia	55	9
• Opportunistic infection		
- Any	76	54
- Cytomegalovirus	45	27
- Herpes simplex	38	11
- Pneumocystis carinii	14	21
- M. avium-intracellulare	24	4
- Candidiasis, esophageal	7	9
- Cryptosporidiosis	7	7
- Cryptococcal meningitis	3	2
- Leukoencephalopathy	–	2
• Hypersensitivity Reaction [c]		
- All	14	9
• Cardiovascular		
- Hypotension	17	9
- Bradycardia	3	–
• Peripheral neuropathy		
- Any	79	46
- Severe **	10	2
• Myalgia/arthralgia		
- Any	93	48
- Severe **	14	16
• Gastrointestinal		
- Nausea and vomiting	69	70
- Diarrhea	90	73
- Mucositis	45	20
• Renal (creatinine elevation)		
- Any	34	18
- Severe **	7	5
• Discontinuation for drug toxicity	7	16

a Based on worst course analysis.
b Paclitaxel dose in mg/m² /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 paclitaxel at a dose of 100 mg/m² every 2 weeks. Notably, severe neutropenia (76% versus 35%), febrile neutropenia (55% versus 9%), and opportunistic infections (76% versus 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described 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

Unless otherwise noted, 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 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/m² compared to 27% at a dose of 175 mg/m² ($p=0.05$). In the same study, severe neutropenia (<500 cells/mm³) 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 cyclosphosphamide 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 35/1,074 (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/m² or 175 mg/m² given as 3-hour infusions, 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/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel dose and schedule. In the Phase 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)

In clinical trials, 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.

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 **PANATAXEL®** 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%-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 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 have 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-agent paclitaxel. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34%-51% from course 2 to 10. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for **PANATAXEL®** therapy.

In the Intergroup first-line ovarian carcinoma study, neurotoxicity included reports of neuromotor and neurosensory events. The regimen with paclitaxel 175 mg/m² given by 3-hour infusion plus cisplatin 75 mg/m² 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/m² 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/m², the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m² given by 3-hour infusion (21%) than at a dose of 135 mg/m² 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/m² by 24-hour infusion followed by cisplatin 75 mg/m² 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, 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.

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. Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Renal

Among the patients treated for Kaposi's sarcoma with paclitaxel, five patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other four patients had renal insufficiency with reversible elevations of serum creatinine. Patients with gynecological cancers treated with **PANATAXEL®** 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 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, dehydration, esophigitis, constipation and ascites have been reported. Neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, was 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, Steven-Johnson syndrome and toxic epidermal necrolysis have been reported. 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.

OVERDOSAGE

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

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 **PANATAXEL®** 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 **PANATAXEL®** administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before **PANATAXEL®**, diphenhydramine (or its equivalent) 50 mg I.V. 30 to 60 minutes prior to **PANATAXEL®**, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before **PANATAXEL®**.
For patients with carcinoma of the ovary, the following regimens are recommended:
1. For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks.
a. **PANATAXEL®** administered intravenously over 3 hours at a dose of 175 mg/m² followed by cisplatin at a dose of 75 mg/m²; or
b. **PANATAXEL®** administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin at a dose of 75 mg/m².
2. In patients previously treated with chemotherapy for carcinoma of the ovary, **PANATAXEL®** has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is **PANATAXEL®** 135 mg/m² or 175 mg/m² administered intravenously over 3 hours every 3 weeks.
For patients with carcinoma of the breast, the following regimens are recommended:
1. For the adjuvant treatment of node-positive breast cancer, the recommended regimen is **PANATAXEL®**, at a dose of 175 mg/m² intravenously over 3 hours every 3 weeks for four courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used four courses of doxorubicin and cyclophosphamide.
2. After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, **PANATAXEL®** at a dose of 175 mg/m² 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 **PANATAXEL®** administered intravenously over 24 hours at a dose of 135 mg/m² followed by cisplatin, 75 mg/m².
For patients with AIDS-related Kaposi's sarcoma, **PANATAXEL®** administered at a dose of 135 mg/m² given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m² given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45-50 mg/m²/week). In the two clinical trials evaluating these schedules, the former schedule (135 mg/m² 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/m² 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 one of the three premedication drugs to 10 mg PO (instead of 20 mg PO);
2. Initiate or repeat treatment with **PANATAXEL®** only if the neutrophil count is at least 1,000 cells/mm³;
3. Reduce the dose of subsequent courses of **PANATAXEL®** by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm³ 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 **PANATAXEL®** should not be repeated until the neutrophil count is at least 1,500 cells/mm³ and the platelet count is at least 100,000 cells/mm³. **PANATAXEL®** 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/mm³. Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe peripheral neuropathy during paclitaxel therapy should have dosage reduced by 20% for subsequent courses of **PANATAXEL®**. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Hepatic Impairment

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade III-IV myelosuppression. Recommendations for dosage adjustment for the first course of therapy are shown in Table 9 for both 3 and 24 hour infusion. Further dose reduction in subsequent courses should be based on individual tolerance.Patients should be monitored closely for development of profound myelosuppression.

TABLE 9: RECOMMENDATIONS FOR DOSING IN PATIENTS WITH HEPATIC IMPAIRMENT BASED ON CLINICAL TRIAL DATA[a]

Degree of hepatic impairment			
Transaminase levels		**Bilirubin levels[b]**	**Recommended dose[c]**
24-hour infusion			
<2 x ULN	and	≤1.5 mg/dL	135 mg/m²
2 to <10 x ULN	and	≤1.5 mg/dL	100 mg/m²
<10 x ULN	and	1.6 - 7.5 mg/dL	50 mg/m²
≥10 x ULN	or	>7.5 mg/dL	Not recommended
3-hour infusion			
<10 x ULN	and	≤1.25 x ULN	175 mg/m²
<10 x ULN	and	1.26 - 2.0 x ULN	135 mg/m²
<10 x ULN	and	2.01 - 5.0 x ULN	90 mg/m²
≥10 x ULN	or	>5.0 x ULN	Not recommended

a These recommendations are base on dosages for patients without hepatic impairment of 135 mg/m² over 24 hours or 175 mg/m² 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

PANATAXEL® is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling **PANATAXEL®**. The use of gloves is recommended. If **PANATAXEL®** 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 **PANATAXEL®** 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

PANATAXEL® must be diluted prior to infusion. **PANATAXEL®** 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 IV tubing containing an in-line (0.22 microns) 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.
PANATAXEL® 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.
PANATAXEL® 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.

Stability

Unopened vials of **PANATAXEL®** injection are stable until the date indicated on the package when stored between 2°C to 8°C (36°F to 46°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the **PANATAXEL®** 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.

HOW SUPPLIED

- Vial containing 30 mg of paclitaxel in 5 mL, individually packaged in a carton.
- Vial containing 30 mg of paclitaxel in 5 mL, 5 vial packaged in a carton with one polyethylene infusion set.
- Vial containing 100 mg of paclitaxel in 17 mL, individually packaged in a carton.
- Vial containing 150 mg of paclitaxel in 25 mL, individually packaged in a carton.
- Vial containing 300 mg of paclitaxel in 50 mL, individually packaged in a carton with one polyethylene infusion set.

STORAGE

Should be stored at 2 °C to 8 °C (36 °F to 46 °F). Freezing does not affect this product.

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.

This medication must be used exclusively under medical prescription and surveillance and cannot repeated without a new medical prescription.

This medicine should not be used after the expiry date shown on the pack.

KEEP OUT OF REACH OF CHILDREN

Medicinal specialty authorized by the Argentinean Ministry of Health. Certificate N° 45432.

Manufactured by Bioprofarma S.A.
Bagó Group Member.
Terrada 1270 (C1416ARD)
C. A. de Buenos Aires, Argentina.
www.bioprofarma.com

Laboratorios Bagó S.A.
Current at: March 2012
Package Insert Code: 109PRLIB