

Paclitaxel

PACLIALL

100 mg Lyophilized Powder for
Suspension for IV Infusion
(Albumin-Bound, Nanoparticle)
Antineoplastic



WARNING: NEUTROPENIA

Do not administer PacIALL therapy to patients who have baseline neutrophil counts of less than 1,500 cells/mm³. 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 PacIALL. See Contraindications, Warnings and Precautions and Adverse Reactions.

Note: An albumin form of paclitaxel may substantially affect a drug's functional properties relative to those of drug in solution. DO NOT SUBSTITUTE FOR OR WITH OTHER PACLITAXEL FORMULATIONS.

Composition

Each vial contains:
Paclitaxel USP 100 mg
Albumin Human USP 900 mg

Description

Before reconstitution: White to off-white powder
After reconstitution: Milky and homogenous suspension without any visible particulate matter.

1 INDICATIONS AND USAGE

1.1 Metastatic Breast Cancer

Paclitaxel 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.

1.2 Non-Small Cell Lung Cancer

Paclitaxel is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

1.3 Adenocarcinoma of the Pancreas

Paclitaxel is indicated for the first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

2 DOSAGE AND ADMINISTRATION

2.1 Metastatic Breast Cancer

After failure of combination chemotherapy for metastatic breast cancer or relapse within 6 months of adjuvant chemotherapy, the recommended regimen for paclitaxel is 260 mg/m² administered intravenously over 30 minutes every 3 weeks.

2.2 Non-Small Cell Lung Cancer

The recommended dose of paclitaxel is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of each 21-day cycle. Administer carboplatin on Day 1 of each 21 day cycle immediately after paclitaxel.

2.3 Adenocarcinoma of the Pancreas

The recommended dose of paclitaxel is 125 mg/m² administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after paclitaxel on Days 1, 8 and 15 of each 28-day cycle.

2.4 Dosage in Patients with Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate and severe hepatic impairment treated with paclitaxel may be at increased risk of toxicities known to paclitaxel. Withhold paclitaxel if AST >10 x ULN or bilirubin > 5 x ULN. Recommendations for dosage adjustment for the first course of therapy are shown in Table 1.

For metastatic breast cancer, the dose of paclitaxel can be increased from 130 mg/m² up to 200 mg/m² in patients with severe hepatic impairment in subsequent cycles based on individual tolerance.

For non-small cell lung cancer, reduce the dose of paclitaxel to 50 mg/m² in patients with severe hepatic impairment. In subsequent cycles, the dose of paclitaxel may be increased to 75 mg/m² as tolerated. Monitor patients closely.

Table 1: Recommendations for Starting Dose in Patients with Hepatic Impairment

	SGOT (AST) Levels	Bilirubin Levels	Paclitaxel Dose*		
			MBC	NSCLC*	Pancreatic Adenocarcinoma
Mild	<10 x ULN	AND >1.0 to <1.25 x ULN	260 mg/m ²	100 mg/m ²	125 mg/m ²
Moderate	<10 x ULN	AND 1.26 to 2 x ULN	200 mg/m ²	75 mg/m ²	not recommended
Severe	<10 x ULN	AND 2.01 to 5 x ULN	130 mg/m ²	50 mg/m ²	not recommended
	>10 x ULN	OR > 5 x ULN	not recommended	not recommended	not recommended

MBC = Metastatic Breast Cancer; NSCLC = Non-Small Cell Lung Cancer.
*Dosage recommendations are for the first course of therapy. The need for further dose adjustments in subsequent courses should be based on individual tolerance.

* A dose increase to 200 mg/m² in subsequent courses should be considered based on individual tolerance.
* Patients with bilirubin levels above the upper limit of normal were excluded from clinical trials for pancreatic or lung cancer.

2.5 Dose Reduction/Discontinuation Recommendations

Metastatic Breast Cancer

Patients who experience severe neutropenia (neutrophil <500 cells/mm³ for a week or longer) or severe sensory neuropathy during paclitaxel therapy should have dos age reduced to 220 mg/m² for subsequent courses of paclitaxel. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m². For Grade 3 sensory neuropathy hold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses of paclitaxel.

Non-Small Cell Lung Cancer

• Do not administer paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is atleast 1500 cells/mm³ and platelet count is atleast 100,000 cells/mm³.

• In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an absolute neutrophil count of at least 500 cells/mm³ and platelet count of atleast 50,000 cells/mm³ on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce paclitaxel and carboplatin doses as outlined in Table 2.

• Withhold paclitaxel for Grade 3-4 peripheral neuropathy. Resume paclitaxel and carboplatin at reduced doses (see Table 2) when peripheral neuropathy improves to Grade 1 or completely resolves.

Table 2: Permanent Dose Reductions for Hematologic and Neurologic Adverse Drug Reactions in NSCLC

Adverse Drug Reaction	Occurrence	Weekly Paclitaxel Dose (mg/m ²)	Every 3-Week Carboplatin Dose (AUC mg-min/mL)
Neutropenic Fever (ANC less than 500/mm ³ with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm ³ OR ANC less than 500/mm ³ for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm ³	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Adenocarcinoma of the Pancreas

Dose level reductions for patients with adenocarcinoma of the pancreas, as referenced in Tables 4 and 5, are provided in Table 3.

Table 3: Dose Level Reductions for Patients with Adenocarcinoma of the Pancreas

Dose Level	Paclitaxel (mg/m ²)	Gemcitabine (mg/m ²)
Full dose	125	1000
1 st dose reduction	100	800
2 nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Recommended dose modifications for neutropenia and thrombocytopenia for patients with adenocarcinoma of the pancreas are provided in Table 4.

Table 4: Dose Recommendation and Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle for Patients with Adenocarcinoma of the Pancreas

Cycle Day	ANC (cells/mm ³)	Platelet count (cells/mm ³)	Paclitaxel / Gemcitabine
Day 1	<1500	OR <100,000	Delay doses until recovery
Day 8	500 to <1000	OR 50,000 to <75,000	Reduce 1 dose level
	<500	OR <50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:			
	500 to <1000	OR 50,000 to <75,000	Reduce 1 dose level from Day 8
	<500	OR <50,000	Withhold doses
Day 15: If Day 8 doses were withheld:			
	≥1000	OR ≥75,000	Reduce 1 dose level from Day 1
	500 to <1000	OR 50,000 to <75,000	Reduce 2 dose levels from Day 1
	<500	OR <50,000	Withhold doses

Abbreviations: ANC = Absolute Neutrophil Count

Recommended dose modifications for other adverse drug reactions in patients with adenocarcinoma of the pancreas are provided in Table 5.

Table 5: Dose Modifications for Other Adverse Drug Reactions in Patients with Adenocarcinoma of the Pancreas

Adverse Drug Reaction	Paclitaxel	Gemcitabine
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥1500; resume at next dose level	
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity: Grade 3 or 4	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

2.6 Preparation and Administration Precautions

Paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of paclitaxel. Premedication may be needed in patients who have had prior hypersensitivity reactions to paclitaxel. Patients who experience a severe hypersensitivity reaction to paclitaxel should not be re-challenged with this drug.

2.7 Preparation for Intravenous Administration

Paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use.

AVOID ERRORS, READ ENTIRE PREPARATION INSTRUCTIONS PRIOR TO RECONSTITUTION.

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.



3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel.

Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted paclitaxel into an empty, sterile intravenous bag (plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag). The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer paclitaxel infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2.8 Stability

Unopened vials of paclitaxel are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted paclitaxel in the vial should be used immediately, but may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from bright light for a maximum of 24 hours.

The total combined refrigerated storage time of reconstituted paclitaxel in the vial and in the infusion bag is 24 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension: lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution.

4 CONTRAINDICATIONS

- Paclitaxel should not be used in patients who have baseline neutrophil counts of <1,500 cells/mm³.
- Patients who experience a severe hypersensitivity reaction to paclitaxel should not be re-challenged with the drug.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic Effects

Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of Paclitaxel. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer (MBC), 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Monitor for myelotoxicity by performing complete blood cell counts frequently, including prior to dosing on Day 1 (for MBC) and Days 1, 8, and 15 (for NSCLC and for pancreatic cancer). Do not administer paclitaxel to patients with baseline absolute neutrophil counts (ANC) of less than 1,500 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of paclitaxel therapy, reduce the dose of paclitaxel in subsequent courses in patients with either MBC or NSCLC.

In patients with MBC, resume treatment with every 3-week cycles of paclitaxel after ANC recovers to a level >1,500 cells/mm³ and platelets recover to a level >100,000 cells/mm³.

In patients with NSCLC, resume treatment if recommended (see Dosage and Administration, Table 2) at permanently reduced doses if or both weekly paclitaxel and every 3-week carboplatin after ANC recovers to at least 1500 cells/mm³ and platelet count of at least 100,000 cells/mm³ on Day 1 or to an ANC of at least 500 cells/mm³ and platelet count of at least 50,000 cells/mm³ on Days 8 or 15 of the cycle.

In patients with adenocarcinoma of the pancreas, withhold paclitaxel and gemcitabine if the ANC is less than 500 cells/mm³ or platelets are less than 50,000 cells/mm³ and delay initiation of the next cycle if the ANC is less than 1500 cells/mm³ or platelet count is less than 100,000 cells/mm³ on Day 1 of the cycle. Resume treatment with appropriate dose reduction if recommended.

5.2 Nervous System

Sensory neuropathy is dose- and schedule-dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If a Grade 3 sensory neuropathy develops, withhold paclitaxel treatment until resolution to Grade 1 or 2 for metastatic breast cancer or until resolution to ≤ Grade 1 for NSCLC and pancreatic cancer followed by a dose reduction for all subsequent courses of paclitaxel.

5.3 Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received paclitaxel in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) initiate treatment with broad spectrum antibiotics. For febrile neutropenia, interrupt paclitaxel and gemcitabine until fever resolves and ANC ≥1500, then resume treatment at reduced dose levels.

5.4 Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving paclitaxel in combination with gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with paclitaxel and gemcitabine.

5.5 Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to paclitaxel should not be re-challenged with this drug.

5.6 Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of paclitaxel in patients with hepatic impairment should be performed with caution. The starting dose should be reduced for patients with moderate or severe hepatic impairment.

5.7 Albumin (Human)

Paclitaxel contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

5.8 Use in Pregnancy

Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryo-fetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations. There are no adequate and well-controlled studies in pregnant women receiving paclitaxel. If this drug 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 while receiving paclitaxel.

5.9 Use in Men

Men should be advised not to father a child while receiving paclitaxel.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions (≥20%) with single-agent use of paclitaxel in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea.

The most common adverse reactions (≥20%) of paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue/see

Adverse Reactions (6.2). The most common serious adverse reactions of paclitaxel in combination with carboplatin for non-small cell lung cancer are anemia (4%) and pneumonia (3%). The most common adverse reactions resulting in permanent discontinuation of paclitaxel are neutropenia (3%), thrombocytopenia (3%), and peripheral neuropathy (1%). The most common adverse reactions resulting in dose reduction of paclitaxel are neutropenia (24%), thrombocytopenia (13%), and anemia (6%). The most common adverse reactions leading to withholding or delay in paclitaxel dosing are neutropenia (41%), thrombocytopenia (30%), and anemia (16%).

In a randomized open-label trial of paclitaxel in combination with gemcitabine for pancreatic adenocarcinoma, the most common (≥20%) selected (with a ≥5% higher incidence) adverse reactions of paclitaxel are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash, and dehydration. The most common serious adverse reactions of paclitaxel (with a ≥1% higher incidence) are pyrexia (6%), dehydration (5%), pneumonia (4%) and vomiting (4%). The most common adverse reactions resulting in permanent discontinuation of paclitaxel are peripheral neuropathy (8%), fatigue (4%) and thrombocytopenia (2%). The most common adverse reactions resulting in dose reduction of paclitaxel are neutropenia (10%) and peripheral neuropathy (6%). The most common adverse reactions leading to withholding or delay in paclitaxel dosing are neutropenia (16%), thrombocytopenia (12%), fatigue (8%), peripheral neuropathy (15%), anemia (5%) and diarrhea (5%).

6.1 Clinical Trials Experience in Metastatic Breast Cancer

Table 6 shows the frequency of important adverse events in the randomized comparative trial for the patients who received either single-agent paclitaxel or paclitaxel injection for the treatment of metastatic breast cancer.

Table 6: Frequency of Important Treatment Emergent Adverse Events in the Randomized Metastatic Breast Cancer Study on an Every-3-Weeks Schedule

	Percent of Patients	
	Paclitaxel 260 mg/m ² over 30 min (n=225)	Paclitaxel Injection 175 mg/m ² over 3 h ^a (n=225)
Bone marrow		
Neutropenia <2.0 x 10 ⁹ /L, <0.5 x 10 ⁹ /L	80 9	82 22
Thrombocytopenia <100 x 10 ⁹ /L, <50 x 10 ⁹ /L	2 <1	3 <1
Anemia <11 g/L, <8 g/L	33 1	25 <1
Infections	24	20
Febrile Neutropenia	2	1
Neutropenic Sepsis	<1	<1
Bleeding	2	2
Hypersensitivity Reaction^b		
All	4	12
Severe ^c	0	2
Cardiovascular		
Vital Sign Changes During Administration		
Bradycardia	<1	<1
Hypotension	5	5
Severe Cardiovascular Events ^d	3	4
Abnormal ECG		
All Patients	60	52
Patients with Normal Baseline	35	30
Respiratory		
Cough	7	6
Dyspnea	12	9
Sensory Neuropathy		
Any Symptoms	71	56
Severe Symptoms ^e	10	2
Myalgia / Arthralgia		
Any Symptoms	44	49
Severe Symptoms ^e	8	4
Asthenia		
Any Symptoms	47	39
Severe Symptoms ^e	8	3
Fluid Retention/Edema		
Any Symptoms	10	8
Severe Symptoms ^e	0	<1
Gastrointestinal		
Nausea		
Any Symptoms	30	22
Severe Symptoms ^e	3	<1
Vomiting		
Any Symptoms	18	10
Severe Symptoms ^e	4	1
Diarrhea		
Any Symptoms	27	15
Severe Symptoms ^e	<1	1
Mucositis		
Any Symptoms	7	6
Severe Symptoms ^e	<1	0
Alopecia	90	94
Hepatic (Patients with Normal Baseline)		
Bilirubin Elevations	7	7
Alkaline Phosphatase Elevations	36	31
AST (SGOT) Elevations	39	32
Injection Site Reaction	<1	1

^a Based on worst grade by NCI Common Terminology Criteria for Adverse Events (CTCAE) version 2.

^b Paclitaxel injection patients received premedication.

^c Includes treatment-related events related to hypersensitivity (e.g., flushing, dyspnea, chest pain, hypotension) that began on a day of dosing.

^d Severe events are defined as at least grade 3 toxicity.

Adverse Event Experiences by Body System

Table 9: Selected Hematologic Laboratory-Detected Abnormalities with a Higher Incidence (≥ 5% for Grades 1-4 or ≥ 2% for Grades 3-4 Events) in the Paclitaxel/Gemcitabine Arm

	Paclitaxel (125 mg/m ² / Gemcitabine		Gemcitabine	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Neutropenia ^a	73	38	58	27
Thrombocytopenia ^a	74	13	70	9

^a405 patients assessed in paclitaxel/gemcitabine-treated group
^b388 patients assessed in gemcitabine-treated group
^c404 patients assessed in paclitaxel/gemcitabine-treated group
^dNeutrophil growth factors were administered to 26% of patients in the paclitaxel/gemcitabine group.

Table 10 provides the frequency and severity of adverse reactions which occurred with a difference of ≥ 5% for all grades or ≥ 2% for Grade 3 or higher in the paclitaxel plus gemcitabine-treated group compared to the gemcitabine group.

Table 10: Selected Adverse Reactions with a Higher Incidence (≥ 5% for All Grade Toxicity or ≥ 2 % for Grade 3 or Higher Toxicity) in the Paclitaxel/Gemcitabine Arm

System Organ Class	Adverse Reaction	Paclitaxel (125 mg/m ²) and gemcitabine (N=421)		Gemcitabine (N=402)	
		All Grades	Grades 3 or Higher	All Grades	Grades 3 or Higher
General disorders and administration site conditions	Fatigue	248 (59%)	77 (18%)	183 (46%)	37 (9%)
	Peripheral edema	194 (46%)	13 (3%)	122 (30%)	12 (3%)
	Pyrexia	171 (41%)	12 (3%)	114 (28%)	4 (1%)
	Asthenia	79 (19%)	29 (7%)	54 (13%)	17 (4%)
	Mucositis	42 (10%)	6 (1%)	16 (4%)	1 (< 1%)
Gastrointestinal disorders	Nausea	228 (54%)	27 (6%)	192 (48%)	14 (3%)
	Diarrhea	184 (44%)	26 (6%)	95 (24%)	6 (1%)
	Vomiting	151 (36%)	25 (6%)	113 (28%)	15 (4%)
	Algoria	212 (50%)	6 (1%)	21 (5%)	0
	Flatulence	128 (30%)	8 (2%)	40 (10%)	2 (< 1%)
Skin and subcutaneous tissue disorders	Peripheral neuropathy ^a	227 (54%)	70 (17%)	51 (12%)	3 (1%)
	Dyspareunia	68 (16%)	0	33 (8%)	0
	Headache	60 (14%)	1 (< 1%)	38 (9%)	1 (< 1%)
	Decreased appetite	152 (36%)	23 (5%)	104 (26%)	8 (2%)
	Dehydration	87 (21%)	31 (7%)	45 (11%)	10 (2%)
Respiratory, thoracic and mediastinal disorders	Epistaxis	64 (15%)	1 (< 1%)	14 (3%)	1 (< 1%)
	Urinary tract infection ^b	47 (11%)	10 (2%)	20 (5%)	1 (< 1%)
	Pain in extremity	48 (11%)	3 (1%)	24 (6%)	3 (1%)
	Arthralgia	47 (11%)	3 (1%)	13 (3%)	1 (< 1%)
	Myalgia	44 (10%)	4 (1%)	15 (4%)	0
Psychiatric disorders	Depression	51 (12%)	1 (< 1%)	24 (6%)	0

^a Peripheral neuropathy is defined by the MedDRA Version 15.0 Standard MedDRA Query neuropathy (broad scope).
^b Urinary tract infections includes the preferred terms of: urinary tract infection, cystitis, uropoiesis, urinary tract infection bacterial, and urinary tract infection enterococcal.

Additional clinically relevant adverse reactions that were reported in < 10% of the patients with adenocarcinoma of the pancreas who received paclitaxel/gemcitabine included:

Infections & infestations: oral candidiasis, pneumonia
Vascular disorders: hypertension
Cardiac disorders: tachycardia, congestive cardiac failure
Eye disorders: cystoid macular edema

Peripheral Neuropathy
Grade 3 peripheral neuropathy occurred in 17% of patients who received paclitaxel/gemcitabine compared to 1% of patients who received gemcitabine only; no patients developed grade 4 peripheral neuropathy. The median time to first occurrence of Grade 3 peripheral neuropathy in the paclitaxel arm was 140 days. Upon suspension of paclitaxel dosing, the median time to improvement from Grade 3 peripheral neuropathy to ≤ Grade 1 was 29 days. Of paclitaxel-treated patients with Grade 3 peripheral neuropathy, 44% resumed paclitaxel at a reduced dose.

Sepsis
Sepsis occurred in 5% of patients who received paclitaxel/gemcitabine compared to 2% of patients who received gemcitabine alone. Sepsis occurred both in patients with and without neutropenia. Risk factors for sepsis included biliary obstruction or presence of biliary stent.

Pneumonitis
Pneumonitis occurred in 4% of patients who received paclitaxel/gemcitabine compared to 1% of patients who received gemcitabine alone. Two of 17 patients in the paclitaxel arm with pneumonitis died.

6.4 Other Experiences with Paclitaxel protein bound particles and other Paclitaxel Formulations
Unless otherwise noted, the following discussion refers to the adverse reactions that have been identified during post-approval use of paclitaxel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. In some instances, severe events observed with paclitaxel injection may be expected to occur with paclitaxel.

Hypersensitivity Reactions
Severe and sometimes fatal hypersensitivity reactions have been reported with paclitaxel. The use of paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular
There have been reports of congestive heart failure, left ventricular dysfunction, and atrioventricular block with paclitaxel. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.

Respiratory
There have been reports of pneumonitis, interstitial pneumonia and pulmonary embolism in patients receiving paclitaxel and reports of radiation pneumonitis in patients receiving concurrent radiotherapy. Reports of lung fibrosis have been received as part of the continuing surveillance of paclitaxel injection safety and may also be observed with paclitaxel.

Neurologic
Cranial nerve palsies and vocal cord paresis have been reported, as well as autonomic neuropathy resulting in paralytic ileus.

Vision Disorders
Reports in the literature of abnormal visual evoked potentials in patients treated with paclitaxel injection suggest persistent optic nerve damage. These may also be observed with paclitaxel.

Reduced visual acuity due to cystoid macular edema (CME) has been reported during treatment with paclitaxel as well as with other taxanes. After cessation of treatment, CME improves and visual acuity may return to baseline.

Hepatic
Reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel injection safety and may occur following paclitaxel treatment.

Gastrointestinal (GI)
There have been reports of intestinal obstruction, intestinal perforation, pancreatitis, and ischemic colitis following paclitaxel treatment. There have been reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-

CSF, occurring in patients treated with paclitaxel injection alone and in combination with other chemotherapeutic agents.

Injection Site Reaction
There have been reports of extravasation of paclitaxel. Given the possibility of extravasation, it is advisable to monitor closely the paclitaxel infusion site for possible infiltration during drug administration.

Severe events such as phlebitis, cellulitis, induration, necrosis, and fibrosis have been reported as part of the continuing surveillance of paclitaxel injection safety. In some cases the onset of the injection site reaction in paclitaxel injection patients either occurred during a prolonged infusion or was delayed by a week to ten days. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel injection at a different site, i.e., "recall," has been reported.

Other Clinic of Events
Skin reactions including generalized or maculopapular rash, erythema, and pruritus have been observed with paclitaxel. There have been case reports of photosensitivity reactions, radiation recall phenomenon, and in some patients previously exposed to capecitabine, reports of palmar-plantar erythrodysesthesia. Stevens-Johns on syndrome and toxic epidermal necrolysis have been reported.

There have been reports of conjunctivitis, cellulitis, and increased lacrimation with paclitaxel injection.

6.5 Accidental Exposure
No reports of accidental exposure to paclitaxel have been received. However, upon inhalation of paclitaxel, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

7 DRUG INTERACTIONS
The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. In the absence of other clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D.
There are no adequate and well-controlled studies in pregnant women using paclitaxel. Based on its mechanism of action and findings in animals, paclitaxel can cause fetal harm when administered to a pregnant woman. If this drug 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 while receiving paclitaxel.

Administration of paclitaxel protein-bound particles to rats during pregnancy, on gestation days 7 to 17 at doses of 6 mg/m² (approximately 2% of the daily maximum recommended human dose on a mg/m² basis) caused embryofetal toxicities, as indicated by intrauterine mortality, increased resorptions (up to 5-fold), reduced numbers of litters and live fetuses, reduction in fetal body weight and increase in fetal anomalies. Fetal anomalies included soft tissue and skeletal malformations, such as eye bulge, folded retina, microphthalmia and dilation of brain ventricles. A lower incidence of soft tissue and skeletal malformations were also exhibited at 3 mg/m² (approximately 1% of the daily maximum recommended human dose on a mg/m² basis).

8.3 Nursing Mothers
It is not known whether paclitaxel is excreted in human milk. Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of paclitaxel in pediatric patients have not been evaluated.

8.5 Geriatric Use
Of the 229 patients in the randomized study who received paclitaxel for the treatment of metastatic breast cancer, 13% were at least 65 years of age and < 2% were 75 years or older. No toxicities occurred notably more frequently among patients who received paclitaxel.

Of the 514 patients in the randomized study who received paclitaxel and carboplatin for the first-line treatment of non-small cell lung cancer, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression, peripheral neuropathy, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years old. No overall difference in effectiveness, as measured by response rates, was observed between patients 65 years or older compared to patients younger than 65 years old.

Of the 431 patients in the randomized study who received paclitaxel and gemcitabine for the first-line treatment of pancreatic adenocarcinoma, 41% were 65 years or older and 10% were 75 years or older. No overall differences in effectiveness were observed between patients who were 65 years of age or older and younger patients. Diarrhea, decreased appetite, dehydration and epistaxis were more frequent in patients 65 years or older compared with patients younger than 65 years old. Clinical studies of paclitaxel did not include sufficient number of patients with pancreatic cancer who were 75 years and older to determine whether they respond differently from younger patients.

8.6 Patients with Hepatic Impairment
Because the exposure and toxicity of paclitaxel can be increased in patients with hepatic impairment, the administration of paclitaxel should be performed with caution in patients with hepatic impairment. Paclitaxel protein bound particles has not been studied in combination with gemcitabine for the treatment of pancreatic cancer in patients with a bilirubin greater than the upper limit of normal.

8.7 Patients with Renal Impairment
The use of paclitaxel protein bound particles has not been studied in patients with renal impairment.

10 OVERDOSAGE
There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

11 DESCRIPTION
Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a noncrystalline, amorphous state. Paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Paclitaxel is free of solvents.

The active agent in Paclitaxel is paclitaxel, a microtubule inhibitor. The chemical structure of paclitaxel is 5β,20-Epoxy-1,2α,7β,10β,13α-hexahydroxytax-11-en-9-one, 4,10-dicarbonyl-2-benzoate-13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:

