

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel Injection USP

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Each ml contains:

Paclitaxel USP	6.0 mg
Polyoxyl 35 castor Oil USNF	527.0 mg
Dehydrated alcohol USP	49.7%v/v

### 3. PHARMACEUTICAL FORM

Injection.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

INTAXEL is indicated as first-line and subsequent therapy for the treatment of advanced metastatic carcinoma of the ovary. As first-line therapy, INTAXEL is indicated in combination with cisplatin.

INTAXEL is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

INTAXEL is used in first line treatment of breast cancer after relapse within 6 months of adjuvant chemotherapy. INTAXEL is used as second line therapy after failure of combination chemotherapy for metastatic breast cancer. Each prior therapy should have included an anthracycline unless clinically contraindicated.

INTAXEL, 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.

INTAXEL is indicated for the second-line treatment of AIDS- related Kaposi's sarcoma.

#### 4.2 Posology and method of administration

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

All patients should be premedicated prior to Paclitaxel (INTAXEL) administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Paclitaxel (INTAXEL), diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Paclitaxel (INTAXEL), and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Paclitaxel (INTAXEL).

For patients with **carcinoma of the ovary**, the following regimens are recommended (see CLINICAL STUDIES: Ovarian Carcinoma):

- a) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks.
  - Paclitaxel (INTAXEL) administered intravenously over 3 hours at a dose of 175 mg/m<sup>2</sup> followed by cisplatin at a dose of 75 mg/m<sup>2</sup>; or
  - Paclitaxel (INTAXEL) administered intravenously over 24 hours at a dose of 135 mg/m<sup>2</sup> followed by cisplatin at a dose of 75 mg/m<sup>2</sup>
- b) In patients previously treated with chemotherapy for carcinoma of the ovary, Paclitaxel (INTAXEL) has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is Paclitaxel (INTAXEL) 135 mg/m<sup>2</sup> or 175 mg/m<sup>2</sup> administered intravenously over 3 hours every 3 weeks.

For patients with **carcinoma of the breast**, the following regimens are recommended

- a) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is Paclitaxel (INTAXEL), at a dose of 175 mg/m<sup>2</sup> 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.
- b) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, Paclitaxel (INTAXEL) at a dose of 175 mg/m<sup>2</sup> administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with **non-small cell lung carcinoma**, the recommended regimen, given every 3 weeks, is Paclitaxel (INTAXEL) administered intravenously over 24 hours at a dose of 135 mg/m<sup>2</sup> followed by cisplatin, 75 mg/m<sup>2</sup>.

For patients with **AIDS-related Kaposi's sarcoma**, Paclitaxel (INTAXEL) administered at a dose of 135 mg/m<sup>2</sup> given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m<sup>2</sup> given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45– 50 mg/m<sup>2</sup>/week). In the 2 clinical trials evaluating these schedules (see CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma), the former schedule (135 mg/m<sup>2</sup> every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m<sup>2</sup> 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 Paclitaxel (INTAXEL) only if the neutrophil count is at least 1000 cells/mm<sup>3</sup>;
- 3) Reduce the dose of subsequent courses of Paclitaxel (INTAXEL) by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm<sup>3</sup> for a week or longer); and
- 4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of Paclitaxel (INTAXEL) should not be repeated until the neutrophil count is at least 1,500 cells/mm<sup>3</sup> and the platelet count is at least 100,000 cells/mm<sup>3</sup>. Paclitaxel (INTAXEL) should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm<sup>3</sup>. Patients who experience severe neutropenia (neutrophil <500 cells/mm<sup>3</sup> for a week or longer) or severe peripheral neuropathy during Paclitaxel (INTAXEL) therapy should have dosage reduced by 20% for subsequent courses of Paclitaxel (INTAXEL). 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 the following table for both 3- and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

**Table 18: Recommendations for dosing in patients with Hepatic Impairment<sup>a</sup>:**

Degree of hepatic Impairment			Recommended Paclitaxel dose <sup>c</sup> (mg/m <sup>2</sup> )
Transaminases levels		Bilirubin levels <sup>b</sup>	
<b>24-hour infusion</b>			
< 2 x ULN	and	≤ 1.5 mg/dl	135
2 - < 10 x ULN	and	≤ 1.5 mg/dl	100
< 10 x ULN	and	1.6 – 7.5 mg/dl	50
≥ 10 x ULN	or	> 7.5 mg/dl	Not recommended
<b>3-hour infusion</b>			
< 10 x ULN	and	≤ 1.25 x ULN	175
< 10 x ULN	and	1.26- 2.0 x ULN	135
< 10 x ULN	and	2.01-5.0 x ULN	90
≥ 10 x ULN	or	> 5.0 x ULN	Not recommended

<sup>a</sup> These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m<sup>2</sup> over 24 hours or 175 mg/m<sup>2</sup> over 3 hours.

<sup>b</sup> Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

<sup>c</sup> 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:**

Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Paclitaxel injection (INTAXEL). The use of gloves is recommended. If Paclitaxel injection (INTAXEL) solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If Paclitaxel injection (INTAXEL) 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.

**Preparations for Intravenous Administration:**

Before using the vials allow them to attain room temperature. Prior to infusion Paclitaxel Injection (INTAXEL) 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, solution may show haziness, which is attributed to the formulation vehicle. No significant loss in potency has been noted following simulated delivery of the solution through I.V. tubing containing an inline (0.22 micron) filter.

Published data for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl) phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets such as those, which are polyethylene lined, should be used.

Paclitaxel injection (INTAXEL) should be administered through an in line filter with a microporous membrane not greater than 0.22 microns.

#### 4.3 Contraindications

INTAXEL is contraindicated in patients who have a history of hypersensitivity reactions to Paclitaxel or other drugs formulated in Cremophor® EL (Polyoxyethylated castor oil).

INTAXEL should not be used in solid tumor patients with baseline neutrophil count of  $<1500$  cells/mm<sup>3</sup>. INTAXEL is also contra-indicated in patients having AIDS-related Kaposi's sarcoma with baseline neutrophil count of  $<1000$  cells/mm<sup>3</sup>.

#### 4.4 Special warnings and precautions for use

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusions 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.

Paclitaxel should be administered through an in line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

##### **Hematology:**

Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel. Patients should not be re-treated with subsequent cycles of Paclitaxel until neutrophils recover to a level  $>1500$  cells/mm<sup>3</sup> and platelets recover to a level  $>100,000$  cells/mm<sup>3</sup>. In the case of severe neutropenia ( $<500$  cells/mm<sup>3</sup> for seven days or more) during a course of Paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, Paclitaxel, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm<sup>3</sup>.

##### **Hypersensitivity Reactions:**

Patients with a history of severe hypersensitivity reactions to products containing Paclitaxel or other drugs formulated in Polyoxyl 35 Castor Oil. Should not be treated with Paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with Paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H<sub>2</sub> 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 Paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When Paclitaxel is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

**Nervous System:**

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

Paclitaxel contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol.

**Hepatic:**

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

**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, ie, “recall”, has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of Paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 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.

**Pediatric Use:**

The safety and effectiveness of Paclitaxel in children 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<sup>2</sup> to 420 mg/m<sup>2</sup>. 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.

**Geriatric Use:**

Of 2228 patients who received Paclitaxel in eight clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive Paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In

most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with Paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group. Table 17 presents the incidences of Grade IV neutropenia and severe neuropathy in clinical studies according to age.

**Table: 17 Selected Adverse Events In Geriatric Patients Receiving Paclitaxel In Clinical Studies**

	Patients (n/total [%])			
	Neutropenia (Grade IV)		Peripheral Neuropathy (Grades III/IV)	
INDICATION	Age (y)		Age (y)	
(Study/Regimen)	≥65	<65	≥65	<65
<b>• OVARIAN Cancer</b>				
(Intergroup First-Line/T175/3 c75 <sup>a</sup> )	34/83 (41)	78/252 (31)	24/84 (29) <sup>*b</sup>	46/255 (18) <sup>b</sup>
(GOG-111 First-Line/T135/24 c75 <sup>a</sup> )	48/61 (79)	106/129 (82)	3/62 (5)	2/134 (1)
(Phase 3 Second-Line/T175/3 <sup>c</sup> )	5/19 (26)	21/76 (28)	1/19 (5)	0/76 (0)
(Phase 3 Second-Line/T175/24 <sup>c</sup> )	21/25 (84)	57/79 (72)	0/25 (0)	2/80 (3)
(Phase 3 Second-Line/T135/3 <sup>c</sup> )	4/16 (25)	10/81 (12)	0/17 (0)	0/81 (0)
(Phase 3 Second-Line/T135/24 <sup>c</sup> )	17/22 (77)	53/83 (64)	0/22 (0)	0/83 (0)
(Phase 3 Second-Line Pooled)	47/82 (57) <sup>*</sup>	141/319 (44)	1/83 (1)	2/320 (1)
<b>• Adjuvant BREAST Cancer</b>				
(Intergroup/AC followed by T <sup>d</sup> )	56/102 (55)	734/1468 (50)	5/102 (5) <sup>e</sup>	46/1468 (3) <sup>e</sup>
<b>• BREAST Cancer After Failure of Initial Therapy</b>				
(Phase 3/T175/3c)	7/24 (29)	56/200 (28)	3/25 (12)	12/204 (6)
(Phase 3/T135/3c)	7/20 (35)	37/207 (18)	0/20 (0)	6/209 (3)
<b>• Non-Small Cell LUNG Cancer</b>				
(ECOG/T135/24 c75 <sup>a</sup> )	58/71 (82)	86/124 (69)	9/71 (13) <sup>f</sup>	16/124 (13) <sup>f</sup>
(Phase 3/T175/3 c80a)	37/89 (42) <sup>*</sup>	56/267 (21)	11/91 (12) <sup>*</sup>	11/271 (4)

\* p<0.05

<sup>a</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours; cisplatin doses in mg/m<sup>2</sup>.

<sup>b</sup> Peripheral neuropathy was included within the neurotoxicity category in the Intergroup First-Line Ovarian Cancer study.

<sup>c</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>d</sup> Paclitaxel (T) following 4 courses of doxorubicin and cyclophosphamide (AC) at a dose of 175 mg/m<sup>2</sup>/3 hours every 3 weeks for 4 courses.

<sup>e</sup> Peripheral neuropathy reported as neurosensory toxicity in the Intergroup Adjuvant Breast Cancer study.

<sup>f</sup> Peripheral neuropathy reported as neurosensory toxicity in the ECOG NSCLC study.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have been reported in 2%- 4% of the patients receiving Paclitaxel. Fatal reactions have occurred in patients despite premedication. All the patients should be pretreated with corticosteroids, diphenhydramine and H<sub>2</sub> 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 have been reported at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm<sup>3</sup> (<1000 cells/mm<sup>3</sup> for patients with KS). Frequent monitoring of blood counts should be instituted during Paclitaxel treatment. Patients should not be retreated with subsequent cycles of Paclitaxel until neutrophils recover to a level of >1500 cells/mm<sup>3</sup> and platelets recover to a level of >100,000 cells/mm<sup>3</sup>.

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

#### **4.5 Interaction with other medicinal products**

In a Phase I trial using escalating doses of Paclitaxel (110-200 mg/m<sup>2</sup>) and cisplatin (50 or 75 mg/m<sup>2</sup>) 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. Caution should be exercised when administering Paclitaxel concomitantly with known substrates, inducers (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine), or inhibitors (eg, erythromycin, fluoxetine, gemfibrozil) 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.

#### **4.6 Fertility, pregnancy and lactation**

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<sup>2</sup> basis). At this dose, Paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

##### **Nursing mothers:**

It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon 14-labeled Paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving Paclitaxel therapy.

##### **Pregnancy:**

Paclitaxel may cause foetal 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<sup>2</sup> 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<sup>2</sup> basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If Paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard. Women of child bearing potential should be advised to avoid becoming pregnant.

#### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

#### 4.8 Undesirable effects

The frequency and severity of adverse events are generally similar between patients receiving Paclitaxel for treatment of ovarian, breast, non-small cell lung carcinoma, or Kaposi's Sarcoma.

#### **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 seventy-five patients were treated in eight Phase 2 studies with Paclitaxel doses ranging from 135 to 300 mg/m<sup>2</sup> administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m<sup>2</sup>) and two schedules (3 or 24 hours) of Paclitaxel. Two hundred and thirty-six patients with breast carcinoma received Paclitaxel (135 or 175 mg/m<sup>2</sup>) administered over 3 hours in a controlled study.

**Table 10: Summary<sup>a</sup> of adverse events in patients with solid tumours receiving single agent Paclitaxel injection**

	Percent of patients (n=812)
<b>Bone marrow</b>	
Neutropenia <2,000/mm <sup>3</sup>	90
< 500/mm <sup>3</sup>	52
Leukopenia <4,000/m <sup>3</sup>	90
<1,000/m <sup>3</sup>	17
Thrombocytopenia <100,000/mm <sup>3</sup>	20
<50,000/m <sup>3</sup>	7
Anemia <11g/dl	78
<8 g/dl	16
Infections	30
Bleeding	14
Red cell transfusions	25
Platelet transfusions	2
<b>Hypersensitivity reaction<sup>b</sup></b>	
All	41
Severe*	2
<b>Cardiovascular</b>	
Vital sign changes <sup>c</sup>	

Bradycardia (n=537)	3
Hypotension (n=532)	12
Significant Cardiovascular events	1
<b>Abnormal EEG</b>	
All pts	23
Pts with normal baseline (n=559)	14
<b>Peripheral neuropathy</b>	
Any symptoms	60
Severe symptoms*	3
<b>Myalgia/Arthralgia</b>	
Any symptoms	60
Severe symptoms*	8
<b>Gastrointestinal</b>	
Nausea and vomiting	52
Diarrhea	38
Mucositis	31
<b>Alopecia</b>	87
<b>Hepatic</b> (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
<b>Injection site reaction</b>	13
<sup>a</sup> Based on worst course analysis	
<sup>b</sup> All patients received premedication	
<sup>c</sup> During first 3 hours of infusion	
* Severe effects are defined as at least grade III toxicity	

### Disease-Specific Adverse Event Experiences:

#### First-Line Ovary in Combination:

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

**Table 11: Frequency of important adverse events in the phase 3 first line Ovarian carcinoma studies**

		Percent of Patients			
		Intergroup		GOG-111	
		T175/3 <sup>b</sup> c75 <sup>c</sup> (n=339)	C750 <sup>c</sup> c75 <sup>c</sup> (n=336)	T135/24 <sup>b</sup> c75 <sup>c</sup> (n=196)	C750 <sup>c</sup> c75 <sup>c</sup> (n=213)
<b>Bone Marrow</b>					
—Neutropenia	<2000/mm <sup>3</sup>	91 <sup>d</sup>	95 <sup>d</sup>	96	92
	<500/mm <sup>3</sup>	33 <sup>d</sup>	43 <sup>d</sup>	81 <sup>d</sup>	58 <sup>d</sup>
—Thrombocytopenia	<100,000/mm <sup>3</sup>	21 <sup>d</sup>	33 <sup>d</sup>	26	30
	<50,000/mm <sup>3</sup>	3 <sup>d</sup>	7 <sup>d</sup>	10	9
—Anemia	<11 g/dLf	96	97	88	86

	<8 g/dL	3 <sup>d</sup>	8 <sup>d</sup>	13	9
—Infections		25	27	21	15
—Febrile Neutropenia		4	7	15 <sup>d</sup>	4 <sup>d</sup>
<b>Hypersensitivity Reaction</b>					
—All		11 <sup>d</sup>	6 <sup>d</sup>	8 <sup>d,g</sup>	1 <sup>d,g</sup>
—Severe <sup>†</sup>		1	1	3 <sup>d,g</sup>	— <sup>d,g</sup>
• Neurotoxicity <sup>h</sup>					
—Any symptoms		87 <sup>d</sup>	52 <sup>d</sup>	25	20
—Severe symptoms <sup>†</sup>		21 <sup>d</sup>	2 <sup>d</sup>	3 <sup>d</sup>	— <sup>d</sup>
<b>Nausea and Vomiting</b>					
—Any symptoms		88	93	65	69
—Severe symptoms <sup>†</sup>		18	24	10	11
<b>Myalgia/Arthralgia</b>					
—Any symptoms		60 <sup>d</sup>	27 <sup>d</sup>	9 <sup>d</sup>	2 <sup>d</sup>
—Severe symptoms <sup>†</sup>		6 <sup>d</sup>	1 <sup>d</sup>	1	—
<b>Diarrhea</b>					
—Any symptoms		37 <sup>d</sup>	29 <sup>d</sup>	16 <sup>d</sup>	8 <sup>d</sup>
—Severe symptoms <sup>†</sup>		2	3	4	1
<b>Asthenia</b>					
—Any symptoms		NC	NC	17 <sup>d</sup>	10 <sup>d</sup>
—Severe symptoms <sup>†</sup>		NC	NC	1	1
<b>Alopecia</b>					
—Any symptoms		96 <sup>d</sup>	89 <sup>d</sup>	55 <sup>d</sup>	37 <sup>d</sup>
—Severe symptoms <sup>†</sup>		51 <sup>d</sup>	21 <sup>d</sup>	6	8

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>c</sup> Cyclophosphamide (C) or cisplatin (c) dose in mg/m<sup>2</sup>.

<sup>d</sup> p<0.05 by Fisher exact test.

<sup>e</sup> <130,000/mm<sup>3</sup> in the Intergroup study.

<sup>f</sup> <12 g/dL in the Intergroup study.

<sup>g</sup> All patients received premedication.

<sup>h</sup> In the GOG-111 study, neurotoxicity was collected as peripheral neuropathy and in the Intergroup study, neurotoxicity was collected as either neuromotor or neurosensory symptoms.

<sup>†</sup> 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 12: Frequency<sup>a</sup> of important adverse events in the phase 3 second-line ovarian carcinoma study**

		Percent of Patients			
		175/3 <sup>b</sup> (n=95)	175/24 <sup>b</sup> (n=105)	135/3 <sup>b</sup> (n=98)	135/24 <sup>b</sup> (n=105)
<b>Bone Marrow</b>					
—Neutropenia	<2000/mm <sup>3</sup>	78	98	78	98
	<500/mm <sup>3</sup>	27	75	14	67

—Thrombocytopenia	<100,000/mm <sup>3</sup>	4	18	8	6
	<50,000/mm <sup>3</sup>	1	7	2	1
—Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
—Infections		26	29	20	18
<b>• Hypersensitivity Reaction<sup>c</sup></b>					
—All		41	45	38	45
—Severe <sup>†</sup>		2	0	2	1
<b>Peripheral Neuropathy</b>					
—Any symptoms		63	60	55	42
—Severe symptoms <sup>†</sup>		1	2	0	0
<b>Mucositis</b>					
—Any symptoms		17	35	21	25
—Severe symptoms <sup>†</sup>		0	3	0	2

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>c</sup> All patients received premedication.

<sup>†</sup> Severe events are defined as at least Grade III toxicity

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

### Adjuvant Breast:

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

**Table 13: Frequency<sup>a</sup> of important severe adverse events in the phase 3 Adjuvant breast carcinoma study**

		Percent of Patients			
		Early Population		Total Population	
		AC <sup>c</sup> (n=166)	AC <sup>c</sup> followed by T <sup>d</sup> (n=159)	AC <sup>c</sup> (n=1551)	AC <sup>c</sup> followed by T <sup>d</sup> (n=1570)
<b>• Bone Marrow<sup>e</sup></b>					
—Neutropenia	<500/mm <sup>3</sup>	79	76	48	50
—Thrombocytopenia	<50,000/mm <sup>3</sup>	27	25	11	11
—Anemia	<8 g/dL	17	21	8	8
—Infections		6	14	5	6
—Fever Without Infection		—	3	<1	1
• Hypersensitivity Reaction <sup>f</sup>		1	4	1	2
• Cardiovascular Events		1	2	1	2
• Neuromotor Toxicity		1	1	<1	1
• Neurosensory Toxicity		—	3	<1	3

• <b>Myalgia/Arthralgia</b>		—	2	<1	2
• <b>Nausea/Vomiting</b>		13	18	8	9
• <b>Mucositis</b>		13	4	6	5

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> Severe events are defined as at least Grade III toxicity.

<sup>c</sup> Patients received 600 mg/m<sup>2</sup> cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m<sup>2</sup>, 75 mg/m<sup>2</sup>, or 90 mg/m<sup>2</sup> (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for 4 courses.

<sup>d</sup> Paclitaxel following 4 courses of AC at a dose of 175 mg/m<sup>2</sup>/3 hours every 3 weeks for 4 courses.

<sup>e</sup> The incidence of febrile neutropenia was not reported in this study.

<sup>f</sup> All patients were to receive premedication.

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

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

#### **Breast Cancer after Failure of Initial Chemotherapy:**

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

**Table 14: Frequency<sup>a</sup> of important adverse events in the phase 3 study of Breast cancer after failure of initial chemotherapy or within 6 months of adjuvant chemotherapy**

		Percent of Patients	
		175/3 <sup>b</sup> (n=229)	135/3 <sup>b</sup> (n=229)
<b>Bone Marrow</b>			
—Neutropenia	<2000/mm <sup>3</sup>	90	81
	<500/mm <sup>3</sup>	28	19
—Thrombocytopenia	<100,000/mm <sup>3</sup>	11	7
	<50,000/mm <sup>3</sup>	3	2
—Anemia	<11 g/dL	55	47
	<8 g/dL	4	2
—Infections		23	15
—Febrile Neutropenia		2	2
• <b>Hypersensitivity Reaction<sup>c</sup></b>			
—All		36	31
—Severe <sup>†</sup>		0	<1

• Peripheral Neuropathy			
—Any symptoms		70	46
—Severe symptoms†		7	3
Mucositis			
—Any symptoms		23	17
—Severe symptoms†		3	<1

<sup>a</sup>  
Based on worst

course analysis.

<sup>b</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours.

<sup>c</sup> All patients received premedication.

<sup>†</sup> Severe events are defined as at least Grade III toxicity

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

### First-Line NSCLC in Combination:

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

The following table shows the incidence of important adverse events.

**Table 15: Frequency<sup>a</sup> of Important Adverse Events In The Phase 3 Study For First-Line NSCLC**

		Percent of Patients		
		T135/24 <sup>b</sup> c75 (n=195)	T250/24 <sup>c</sup> c75 (n=197)	VP100 <sup>d</sup> c75 (n=196)
<b>Bone Marrow</b>				
—Neutropenia	<2000/mm <sup>3</sup>	89	86	84
	<500/mm <sup>3</sup>	74 <sup>e</sup>	65	55
—Thrombocytopenia	<normal	48	68	62
	<50,000/mm <sup>3</sup>	6	12	16
—Anemia	<normal	94	96	95
	<8 g/dL	22	19	28
—Infections		38	31	35
<b>• Hypersensitivity Reaction<sup>f</sup></b>				
—All		16	27	13
—Severe†		1	4 <sup>e</sup>	1
<b>• Arthralgia/Myalgia</b>				
—Any symptoms		21 <sup>e</sup>	42 <sup>e</sup>	9
—Severe symptoms†		3	11	1
<b>Nausea/Vomiting</b>				
—Any symptoms		85	87	81
—Severe symptoms†		27	29	22
<b>Mucositis</b>				
—Any symptoms		18	28	16

—Severe symptoms†		1	4	2
<b>Neuromotor Toxicity</b>				
—Any symptoms		37	47	44
—Severe symptoms†		6	12	7
<b>Neurosensory Toxicity</b>				
—Any symptoms		48	61	25
—Severe symptoms†		13	28 <sup>e</sup>	8
<b>Cardiovascular Events</b>				
—Any symptoms		33	39	24
—Severe symptoms†		13	12	8

<sup>a</sup> Based on worst course analysis.

<sup>b</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours; cisplatin (c) dose in mg/m<sup>2</sup>.

<sup>c</sup> Paclitaxel dose in mg/m<sup>2</sup>/infusion duration in hours with G-CSF support; cisplatin dose in mg/m<sup>2</sup>.

<sup>d</sup> Etoposide (VP) dose in mg/m<sup>2</sup> was administered IV on days 1, 2, and 3; cisplatin dose in mg/m<sup>2</sup>.

<sup>e</sup> p<0.05.

<sup>f</sup> All patients received premedication.

<sup>†</sup> Severe events are defined as at least Grade III toxicity.

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

#### Kaposi's Sarcoma:

The following table shows the frequency of important adverse events in the 85 patients with KS treated with two different single-agent Paclitaxel regimens.

**Table 16 :Frequency<sup>a</sup> of Important Adverse Events in the AIDS-Related Kaposi's Sarcoma Studies**

	Percent of patients	
	Study CA139-174 Paclitaxel 135/3 <sup>b</sup> q3 wk (n=29)	Study CA139-281 Paclitaxel 100/3 <sup>b</sup> q2 wk (n=56)
<b>Bone marrow</b>		
Neutropenia <2,000/mm <sup>3</sup>	100	95
< 500/mm <sup>3</sup>	76	35
Thrombocytopenia <100,000/mm <sup>3</sup>	52	27
<50,000/m <sup>3</sup>	17	5
Anemia <11g/dl	86	73
<8 g/dl	34	25
Febrile neutropenia	55	9
<b>Opportunistic Infection</b>		
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

<b>Hypersensitivity reaction<sup>c</sup></b>		
All	14	9
<b>Cardiovascular</b>		
Hypertension	17	9
Bradycardia	3	-
<b>Peripheral neuropathy</b>		
Any	79	46
Severe *	10	2
<b>Myalgia/Arthralgia</b>		
Any	93	48
Severe *	14	16
<b>Gastrointestinal</b>		
Nausea and vomiting	69	70
Diarrhea	90	73
Mucositis	45	20
<b>Renal (creatinine elevation)</b>		
Any	34	18
Severe*	7	5
<b>Discontinuation for drug toxicity</b>	7	16
<sup>a</sup> Based on worst course analysis <sup>b</sup> Paclitaxel dose in mg/m <sup>2</sup> /infusion duration in hours <sup>c</sup> all patients received premedication * Severe effects 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/m<sup>2</sup> every 3 weeks than in the study utilizing Paclitaxel at a dose of 100 mg/m<sup>2</sup> every 2 weeks. Notably, severe neutropenia (76% vs 35%), febrile neutropenia (55% vs 9%), and opportunistic infections (76% vs 54%) were more common with the former dose and schedule. The differences between the 2 studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. Note also that only 26% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on Paclitaxel metabolism has not yet been studied.

#### **Adverse Event Experiences by Body System:**

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 are described. 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 trend of 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/mm<sup>3</sup> in 14% of the patients treated with a dose of 135 mg/m<sup>2</sup> compared to 27% at a dose of 175 mg/m<sup>2</sup> (p=0.05). In the same study, severe neutropenia (<500 cells/mm<sup>3</sup>) 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/m<sup>2</sup>/24 hours in combination with cisplatin versus the control arm of cyclophosphamide plus cisplatin, the incidences of grade IV neutropenia and of febrile neutropenia were significantly greater in the Paclitaxel plus cisplatin arm than in the control arm. Grade IV neutropenia occurred in 81% on the Paclitaxel plus cisplatin arm versus 58% on the cyclophosphamide plus cisplatin arm, and febrile neutropenia occurred in 15% and 4% respectively. On the Paclitaxel/cisplatin arm, there were 35/1074 (3%) courses with fever in which Grade IV neutropenia was reported at some time during the course. When Paclitaxel followed by cisplatin was administered to patients with advanced NSCLC in the ECOG study, the incidences of Grade IV neutropenia were 74% (Paclitaxel 135 mg/m<sup>2</sup>/24 hours followed by cisplatin) and 65% (Paclitaxel 250 mg/m<sup>2</sup>/24 hours followed by cisplatin and G-CSF) compared with 55% in patients who received cisplatin/etoposide.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m<sup>2</sup> or 175 mg/m<sup>2</sup> 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 uncommon, and almost never severe (<50,000 cells/mm<sup>3</sup>). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm<sup>3</sup> at least once while on treatment; 7% had a platelet count <50,000 cells/mm<sup>3</sup> at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the Paclitaxel Injection dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no patients treated with the 3-hour infusion received platelet transfusions. In the adjuvant breast carcinoma trial, the incidence of severe thrombocytopenia and platelet transfusions increased with higher doses of doxorubicin.

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

#### **Hypersensitivity Reactions (HSRs):**

All patients received premedication prior to Paclitaxel. The frequency and severity of HSRs were not affected by the dose or schedule of Paclitaxel administration. In the Phase 3 second-line ovarian study, the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients.

These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of Paclitaxel infusion. The most frequent symptoms observed during these severe reactions were

dyspnea, flushing, chest pain, and tachycardia. Abdominal pain, pain in the extremities, diaphoresis, and hypertension were also noted.

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

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

#### **Cardiovascular:**

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

Significant cardiovascular events possibly related to single-agent Paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with Paclitaxel at 175 mg/m<sup>2</sup> 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 rarely. Congestive heart failure, including cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure, has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Atrial fibrillation and supraventricular tachycardia have been reported.

#### **Respiratory:**

Rare reports of interstitial pneumonia, lung fibrosis, and pulmonary embolism have been received as part of the continuing surveillance of Paclitaxel safety. Rare reports of radiation pneumonitis have been received 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 Paclitaxel therapy.

In the Intergroup first-line ovarian carcinoma study, neurotoxicity included reports of neuromotor and neurosensory events. The regimen with Paclitaxel 175 mg/m<sup>2</sup> given by 3-hour infusion plus cisplatin 75 mg/m<sup>2</sup> 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/m<sup>2</sup> given by 24-hour infusion plus cisplatin 75 mg/m<sup>2</sup> 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 is given in combination with cisplatin 75 mg/m<sup>2</sup>, the incidence of severe neurotoxicity is more common at a Paclitaxel dose of 175 mg/m<sup>2</sup> given by 3-hour infusion (21%) than at a dose of 135 mg/m<sup>2</sup> 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 Injection. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving Paclitaxel 135 mg/m<sup>2</sup> by 24-hour infusion followed by cisplatin 75 mg/m<sup>2</sup> 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 has 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.

Convulsions, dizziness, and headache have been reported.

#### **Arthralgia/Myalgia:**

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

#### **Hepatic:**

No relationship was observed between liver function abnormalities and either dose or schedule of Paclitaxel administration. Among patients with normal baseline liver function 7%, 22%, and 19% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Prolonged exposure to Paclitaxel was not associated with cumulative hepatic toxicity.

Hepatic necrosis and hepatic encephalopathy leading to death have 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 Paclitaxel and cisplatin may have an increased risk of renal failure with the combination therapy of Paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

**Gastrointestinal:**

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, esophagitis, 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, ie, "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 10 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.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been received as part of the continuing surveillance of Paclitaxel safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of Paclitaxel safety. In the Phase 3 trial of Paclitaxel 135 mg/m<sup>2</sup> over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/ cisplatin.

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

**Accidental Exposure:**

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

**4.9 Overdose**

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

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

**5.2 Pharmacokinetic properties**

Following intravenous administration of Paclitaxel, the drug exhibited a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of Paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of Paclitaxel following 3- and 24-hour infusions of Paclitaxel at dose levels of 135 and 175 mg/m<sup>2</sup> 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 <sup>2</sup> )	Infusion duration (h)	N (patients)	C <sub>max</sub> (ng/ml)	AUC (0-∞) (ng.h/ml)	CL <sub>T</sub> (L/h/m <sup>2</sup> )	T <sub>1/2</sub> (h)
135	24	2	195	6300	21.7	52.7
175	24	4	365	7993	23.8	15.7
135	3	7	2170	7952	17.7	13.1
175	3	5	3650	15007	12.2	20.2

C<sub>max</sub> = Maximum plasma concentration  
AUC<sub>(0-∞)</sub> = Area under the plasma concentration-time curve from time 0 to infinity  
CL<sub>T</sub> = Total body clearance

It appeared that with the 24-hour infusion of Paclitaxel, a 30% increase in dose (135 mg/m<sup>2</sup> vs 175 mg/m<sup>2</sup>) increased the C<sub>max</sub> by 87%, whereas the AUC<sub>(0-∞)</sub> remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the C<sub>max</sub> and AUC<sub>(0-∞)</sub> 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<sup>2</sup>, indicating extensive extravascular distribution and/or tissue binding of Paclitaxel.

The pharmacokinetics of Paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m<sup>2</sup> given by 1-hour infusions (n=15), 30 to 275 mg/m<sup>2</sup> given by 6-hour infusions (n=36), and 200 to 275 mg/m<sup>2</sup> given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CL<sub>T</sub> 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.

After intravenous administration of 15-275 mg/m<sup>2</sup> doses of Paclitaxel Injection as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m<sup>2</sup> 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 was inhibited 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 disposition and toxicity of Paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma Paclitaxel exposure in patients with abnormal serum bilirubin  $\leq 2$  times upper limit of normal (ULN) administered 175 mg/m<sup>2</sup> was increased, but with no apparent increase in the frequency or severity of toxicity. In five patients with serum total bilirubin  $> 2$  times ULN, there was a statistically non-significant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m<sup>2</sup>), but no observed increase in plasma exposure. The effect of renal dysfunction on the disposition of Paclitaxel has not been investigated.

### 5.3 Preclinical safety data

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<sup>2</sup> basis). At this dose, Paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Polyoxyl 35 castor Oil USNF

Dehydrated alcohol USP

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

### Vial before opening

24 months

### After opening before dilution

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C following multiple needle entries and product withdrawal. Other in-use storage times and conditions are the responsibility of the user.

### After dilution

Prior to infusion Paclitaxel Injection (INTAXEL) 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.

After dilution the solution is for single use only.

## 6.4 Special precautions for storage

Store below 25°C. Protect from light.

## 6.5 Nature and contents of container

INTAXEL (Paclitaxel Injection USP) is supplied as 30mg/5ml in 5ml glass vials, 100mg/16.7ml in 20ml glass vials, 150mg/25ml in 30 ml glass vials, 260mg/43.4ml in 50 ml glass vials and 300mg/50ml in 50ml glass vials.

## 6.6 Special precautions for disposal and other handling

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 are necessary or appropriate.

Paclitaxel is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling Paclitaxel. The use of gloves is recommended. If Paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If Paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Use of 5% sodium hypochlorite or 10% sodium hydroxide solution is recommended as neutralizing agent in cases of spills or leak of this solution.

## 7. MANUFACTURER AND MARKETING AUTHORISATION HOLDER

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**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT : 01/2013**

**11. VERSION NUMBER: MGE/00/2013**