

requires a dose reduction of 20% for all subsequent courses of ONXOL.

ONXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **"PRECAUTIONS: Pediatric Use"** section.)

Hepatic: There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering ONXOL to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of ONXOL has not been studied. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test of CHO/HGPRT gene mutation assay.

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

Pregnancy: Pregnancy Category D. (See **"WARNINGS"** section.)

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 ONXOL therapy.

Pediatric Use: The safety and effectiveness of ONXOL in pediatric patients have not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies:

Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent paclitaxel injection. Two hundred and seventy five patients were treated in eight Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m² administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m²) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six patients with breast carcinoma received paclitaxel (135 or 175 mg/m²) administered over 3 hours in a controlled study.

	Percent of Patients (n=812)	
• Bone Marrow		
- Neutropenia	<2,000/mm ³	90
	<500/mm ³	52
- Leukopenia	<4,000/mm ³	90
	<1,000/mm ³	17
- Thrombocytopenia	<100,000/mm ³	20
	<50,000/mm ³	7
- Anemia	<11g/dL	78
	<8g/dL	30
- Infections		16
- Bleeding		14
- Red Cell Transfusions		25
- Platelet Transfusions		2
• Hypersensitivity Reaction^a		41
- All		2
- Severe ^b		1
• Cardiovascular		
- Vital Sign Changes ^c		
- Bradycardia (N=537)		3
- Hypotension (N=532)		12
- Significant Cardiovascular Events		1
• Abnormal ECG		
- All Pts		23
- Pts with normal baseline (N=559)		14
• Peripheral Neuropathy		
- Any		60
- Severe symptoms ^d		3
• Myalgia/Arthralgia		
- Any		60
- Severe symptoms ^d		6
• Gastrointestinal		
- Nausea and vomiting		52
- Diarrhea		38
- Mucositis		31
• Alopecia		87
• Hepatic (pts with normal baseline and on study data)		
- Bilirubin elevations (N=765)		7
- Alkaline phosphatase elevations (N=575)		22
- AST (SGOT) elevations (N=591)		19
• Injection Site Reaction		13

None of the observed toxicities were clearly influenced by age.

Disease Specific Adverse Event Experiences

Second-Line Ovarian: 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.

	PERCENT OF PATIENTS			
	175/3 ^a (n=95)	175/24 ^b (n=105)	135/3 ^c (n=98)	135/24 ^d (n=105)
• Bone Marrow				
- Neutropenia	<2,000/mm ³	78	98	78
	<500/mm ³	27	75	14
- Thrombocytopenia	<100,000/mm ³	4	18	8
	<50,000/mm ³	1	7	2
- Anemia	<11g/dL	84	90	68
	<8g/dL	11	12	6
- Infections		26	29	20
• Hypersensitivity Reaction^e				
- All		41	45	38
- Severe ^f		2	0	2
• Peripheral Neuropathy				
- Any symptoms		63	60	55
- Severe symptoms ^g		1	2	0
• Mucositis				
- Any symptoms		17	35	21
- Severe symptoms ^g		0	3	0

^a Based on worst course analysis
^b Paclitaxel dose in mg/m²/infusion duration in hours
^c All patients received premedication
^d 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.

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).

	PERCENT OF PATIENTS	
	175/3 ^a (n=229)	135/3 ^b (n=229)
• Bone Marrow		
- Neutropenia	<2,000/mm ³	90
	<500/mm ³	28
- Thrombocytopenia	<100,000/mm ³	11
	<50,000/mm ³	3
- Anemia	<11g/dL	55
	<8g/dL	4
- Infections		23
- Febrile Neutropenia		2
• Hypersensitivity Reaction^c		
- All		36
- Severe ^d		0
• Peripheral Neuropathy		
- Any symptoms		70
- Severe symptoms ^e		3
• Mucositis		
- Any symptoms		23
- Severe symptoms ^e		<1

^a Based on worst course analysis
^b Paclitaxel dose in mg/m²/infusion duration in hours
^c All patients received premedication
^d Severe events are defined as at least Grade III toxicity

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

Adverse Event Experiences By Body System:

The following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in clinical studies. The frequency and severity of important adverse events for the phase 3 ovarian carcinoma and breast carcinoma studies are presented above in tabular form by treatment arm. In addition, rare events have been reported from post-marketing experience or from other clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving paclitaxel for the treatment of ovarian or breast carcinoma.

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 ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm³ in 14% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (<500 cells/mm³) was more frequent with the 24-hour than 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.

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 or 175 mg/m² given as a 3-hour infusion respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm³). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel 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.

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 injection (See **"WARNINGS"** and **"PRECAUTIONS: Hypersensitivity Reactions"** sections). 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 patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period. Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

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 antiarrhythmic therapy.

Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m² over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.

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 antiarrhythmics did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably antineoplastic. (See **PRECAUTIONS: "Drug Interactions"** section.)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.

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.

Neurologic: The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration. 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 to 51% from course 2 to 10.

Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

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

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

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

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

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

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