

**LACHMAN CONSULTANT SERVICES, INC.**  
Westbury, NY 11590

# **ATTACHMENT 3**

**PACKAGE INSERT MODIFICATIONS**

The draft package insert labeling submitted with this petition is based on the approved package insert labeling for the listed drug, Gemzar® (Gemcitabine HCl) for Injection. Differences between the draft package insert and the package insert for Gemzar® are highlighted in color. Descriptions of these changes are as follows:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

At the end of the package insert, provision was made for the inclusion of the name and place of business of the manufacturer and/or distributor and the package insert part number and revision date.

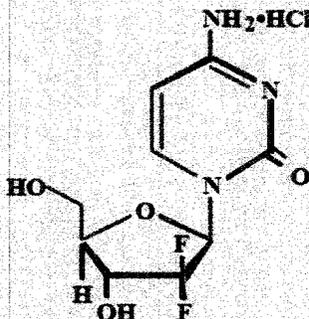
*F02JD6089d*

[REDACTED]

## FOR INJECTION, USP DESCRIPTION

[REDACTED] Hydrochloride is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is  $C_9H_{11}F_2N_3O_4 \cdot HCl$ . It has a molecular weight of 299.66.

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of [REDACTED] for Injection, USP contain either 200 mg, 1 g, [REDACTED] of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg, 1 g [REDACTED] respectively) and sodium acetate (12.5 mg, 62.5 mg [REDACTED], respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

### CLINICAL PHARMACOLOGY

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP.

Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM

T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

**Human Pharmacokinetics** — Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m<sup>2</sup>/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemcitabine dose varied from 500 to 3600 mg/m<sup>2</sup>.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple-dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

**Table 1: Gemcitabine Clearance and Half-Life for the "Typical" Patient**

Age	Clearance	Clearance	Half-Life <sup>a</sup>	Half-Life <sup>a</sup>
	Men (L/hr/m <sup>2</sup> )	Women (L/hr/m <sup>2</sup> )	Men (min)	Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

<sup>a</sup> Half-life for patients receiving a short infusion (<70 min).

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly result in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m<sup>2</sup> following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m<sup>2</sup>, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

**Drug Interactions** — When [REDACTED] (1250 mg/m<sup>2</sup> on Days 1 and 8) and cisplatin (75 mg/m<sup>2</sup> on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m<sup>2</sup> and on Day 8 was 107 L/hr/m<sup>2</sup>. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m<sup>2</sup> with a corresponding half-life of 134 hours (*see Drug Interactions under PRECAUTIONS*).

### CLINICAL STUDIES

**Breast Cancer** — Data from a multi-national, randomized Phase 3 study (529 patients) support the use of [REDACTED] in combination with paclitaxel for treatment of breast cancer patients who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. [REDACTED] 1250 mg/m<sup>2</sup> was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m<sup>2</sup> administered prior to [REDACTED] on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m<sup>2</sup> was administered on Day 1 of each 21-day cycle as the control arm.

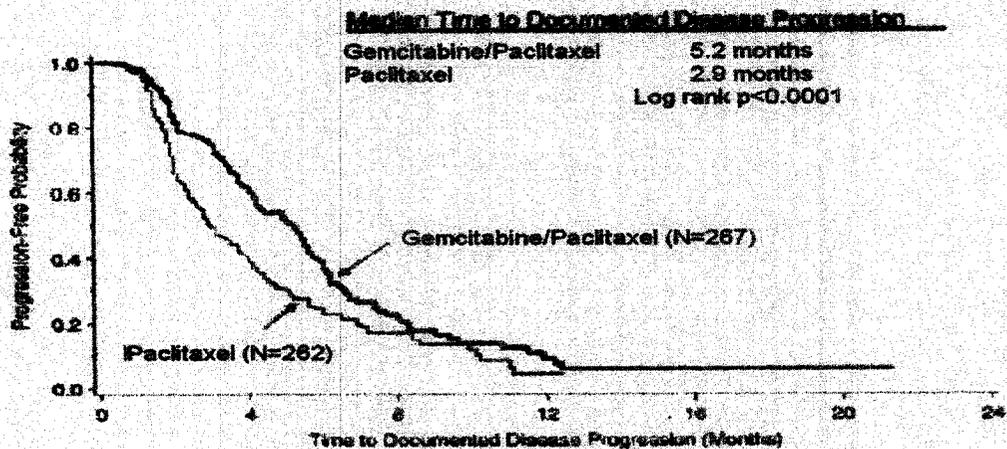
The addition of [REDACTED] to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to monotherapy with paclitaxel as shown in Table 2 and Figure 1. Further, there was a strong trend toward improved survival for the group given [REDACTED] based on an interim survival analysis.

**Table 2: Gemcitabine Plus Paclitaxel Versus Paclitaxel in Breast Cancer**

	Gemcitabine/Paclitaxel	Paclitaxel	
Number of patients	267	262	
Median age, years	53	52	
Range	26 to 83	26 to 75	
Metastatic disease	97.0%	96.9%	
Baseline KPS <sup>1</sup> ≥90	70.4%	74.4%	
Number of tumor sites			
1-2	56.6%	58.8%	
≥3	43.4%	41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	
Time to Documented Disease Progression <sup>2</sup>			p=0.0001
Median (95% C.I.) months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)	
Hazard Ratio (95% C.I.)	0.650 (0.524, 0.805)		p=0.0001
Overall Response Rate <sup>2</sup> (95% C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)	p=0.0001

<sup>1</sup> Karnofsky Performance Status

<sup>2</sup> These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.



**Figure 1: Kaplan-Meier Curve of Time to Documented Disease Progression in [REDACTED] plus Paclitaxel versus Paclitaxel Breast Cancer Study (N=529).**

*Non-Small Cell Lung Cancer (NSCLC)* — Data from 2 randomized clinical studies (657 patients) support the use of [REDACTED] in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

**[REDACTED] plus cisplatin versus cisplatin:** This study was conducted in Europe, the U.S., and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received cycle with cisplatin 100 mg/m<sup>2</sup> administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m<sup>2</sup> was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 3. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the [REDACTED] plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the [REDACTED] plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Logrank p=0.008, two-sided). Median time to disease progression was 5.2 months on the [REDACTED] plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.009, two-sided). The objective response rate on the [REDACTED] plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

**[REDACTED] plus cisplatin versus etoposide plus cisplatin:** A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to [REDACTED] 1250 mg/m<sup>2</sup> on Days 1 and 8, and cisplatin 100 mg/m<sup>2</sup> on Day 1 of a 21-day cycle or to etoposide 100 mg/m<sup>2</sup> I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m<sup>2</sup> on Day 1 on a 21-day cycle (Table 3).

There was no significant difference in survival between the two treatment arms (Logrank p=0.18, two-sided). The median survival was 8.7 months for the [REDACTED] plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the [REDACTED] plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Logrank p=0.015, two-sided). The objective response rate for the [REDACTED] plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

**Quality of Life (QOL):** QOL was a secondary endpoint in both randomized studies. In the [REDACTED] plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of [REDACTED] plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies, no significant differences were observed in QOL between the [REDACTED] plus cisplatin arm and the comparator arm.

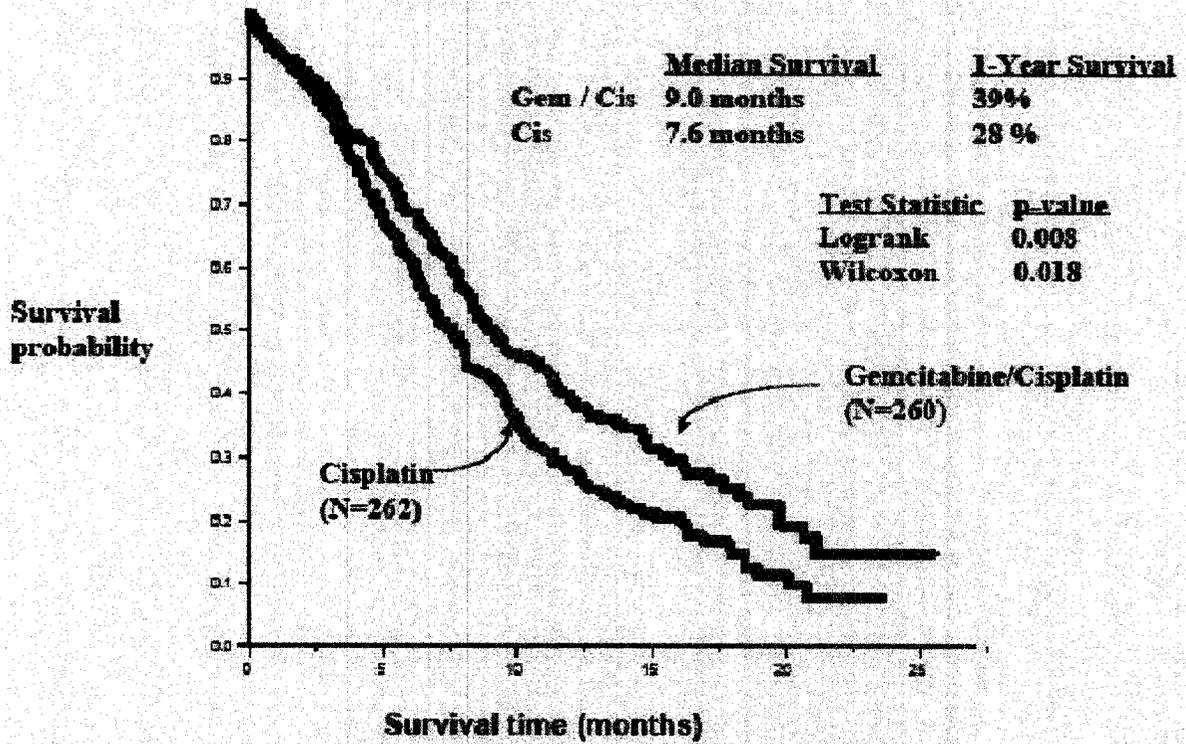


Figure 2: Kaplan-Meier Survival Curve in Gemcitabine plus Cisplatin versus Cisplatin NSCLC Study (N=522)

**Table 3: Randomized Trials of Combination Therapy with Gemcitabine plus Cisplatin in NSCLC**

Trial	28-day Schedule <sup>a</sup>		21-day Schedule <sup>b</sup>		
	Gemcitabine/ Cisplatin	Cisplatin	Gemcitabine/ Cisplatin	Cisplatin/ Etoposide	
Number of patients	260	262	69	66	
Male	182	186	64	61	
Female	78	76	5	5	
Median age, years	62	63	58	60	
Range	36 to 88	35 to 79	33 to 76	35 to 75	
Stage IIIA	7%	7%	N/A	N/A	
Stage IIIB	26%	23%	48%	52%	
Stage IV	67%	70%	52%	49%	
Baseline KPS <sup>c</sup> 70 to 80	41%	44%	45%	52%	
Baseline KPS <sup>c</sup> 90 to 100	57%	55%	55%	49%	

Survival			P=0.008			p=0.18
Median, months	9.0	7.6		8.7	7.0	
(95% C.I.) months	8.2, 11.0	6.6, 8.8		7.8, 10.1	6.0, 9.7	
Time to Disease Progression			P=0.009			p=0.015
Median, months	5.2	3.7		5.0	4.1	
(95% C.I.) months	4.2, 5.7	3.0, 4.3		4.2, 6.4	2.4, 4.5	
Tumor Response	26%	10%	p<0.0001 <sup>d</sup>	33%	14%	p=0.01 <sup>d</sup>

(a) 28-day schedule – Gemcitabine plus cisplatin: Gemcitabine 1000 mg/m<sup>2</sup> on Days 1, 8 and 15 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days.

(b) 21-day schedule – Gemcitabine plus cisplatin: Gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 and I.V. etoposide 100 mg/m<sup>2</sup> on Days 1, 2, and 3 every 21 days.

(c) Karnofsky Performance Status.

(d) p-value for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

N/A Not applicable.

*Pancreatic Cancer* — Data from 2 clinical trials evaluated the use of [REDACTED] in patients with locally advanced or metastatic pancreatic cancer. The first trial compared [REDACTED] to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of [REDACTED] in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of [REDACTED] was administered intravenously at a dose of 1000 mg/m<sup>2</sup> over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with [REDACTED]. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was “clinical benefit response,” which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:

- i) the patient showed a  $\geq 50\%$  reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

- ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain ( $\geq 7\%$  increase maintained for  $\geq 4$  weeks) not due to fluid accumulation.

The first study was a multi-center (17 sites in U.S. and Canada), prospective, single-blinded, two-arm, randomized, comparison of [REDACTED] and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m<sup>2</sup> for 30 minutes. The results from this randomized trial are shown in Table 4. Patients treated with [REDACTED] had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 3. No confirmed objective tumor responses were observed with either treatment.

**Table 4: Gemcitabine Versus 5-FU in Pancreatic Cancer**

	Gemcitabine	5-FU	
Number of patients	63	63	
Male	34	34	
Female	29	29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS <sup>a</sup> ≤70	69.8%	68.3%	

Clinical benefit response	22.2% (N <sup>c</sup> =14)	4.8% (N=3)	p=0.004
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability <sup>b</sup>	(N=30) 46%	(N=19) 29%	
9-month probability <sup>b</sup>	(N=14) 24%	(N=4) 5%	
1-year probability <sup>b</sup>	(N=9) 18%	(N=2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+ months	
95% C.I. of the median	4.7 to 6.9 months	3.1 to 5.1 months	
Time to Disease Progression			p=0.0013
Median	2.1 months	0.9 months	
Range	0.1+ to 9.4 months	0.1 to 12.0+ months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

<sup>a</sup> Karnofsky Performance Status.

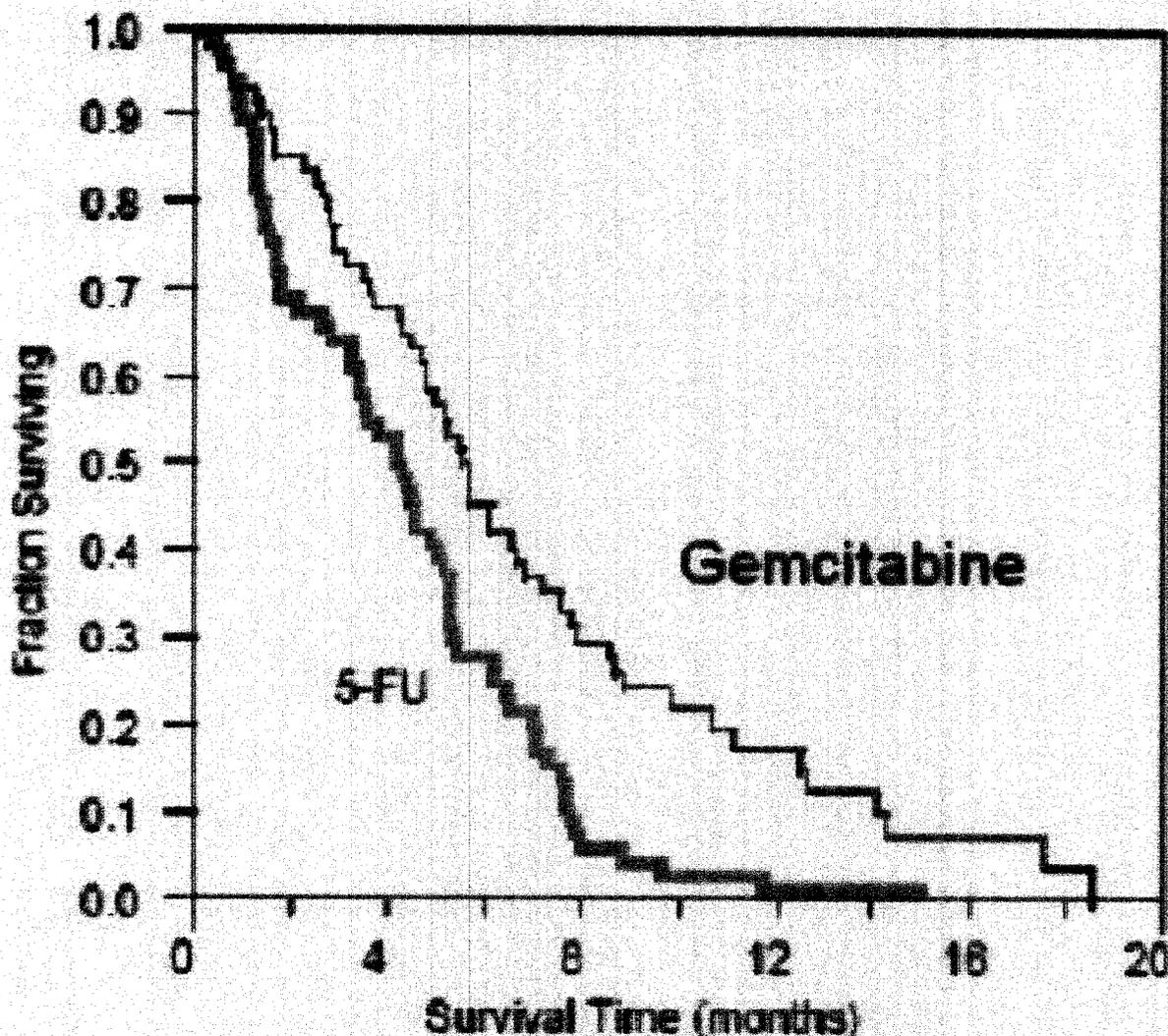
<sup>b</sup> Kaplan Meier estimates.

<sup>c</sup> N=number of patients.

- No progression at last visit; remains alive.

The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

Clinical benefit response was achieved by 14 patients treated with [REDACTED] and 3 patients treated with 5-FU. One patient on the [REDACTED] arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the [REDACTED] arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the [REDACTED] arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.



**Figure 3: Kaplan-Meier Survival Curve.**

The second trial was a multi-center (17 U.S. and Canadian centers), open-label study of ██████████ in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

*Other Clinical Studies* — When ██████████ was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of ██████████ to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m<sup>2</sup>. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m<sup>2</sup> (30-minute infusion) and 150 mg/m<sup>2</sup> (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m<sup>2</sup> at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (*see* CLINICAL PHARMACOLOGY) and the toxicity appears to be increased if

██████████ is administered more frequently than once weekly or with infusions longer than 60 minutes (*see* **WARNINGS**).

## INDICATIONS AND USAGE

### Therapeutic Indications

*Breast Cancer* — ██████████ in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

*Non-Small Cell Lung Cancer* — ██████████ is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

*Pancreatic Cancer* — ██████████ is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. ██████████ is indicated for patients previously treated with 5-FU.

## CONTRAINDICATION

██████████ is contraindicated in those patients with a known hypersensitivity to the drug (*see* *Allergic under* **ADVERSE REACTIONS**).

## WARNINGS

*Caution* — Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing has been shown to increase toxicity (*see* **CLINICAL STUDIES**).

*Hematology* — ██████████ can suppress bone marrow function as manifested by leucopenia, thrombocytopenia, and anemia (*see* **ADVERSE REACTIONS**), and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy. *See* **DOSAGE AND ADMINISTRATION** for recommended dose adjustments.

*Pulmonary* — Pulmonary toxicity has been reported with the use of ██████████. In cases of severe lung toxicity, ██████████ therapy should be discontinued immediately and appropriate supportive care measures instituted (*see* *Pulmonary under* **Single-Agent Use and under Post-marketing experience in** **ADVERSE REACTIONS** section).

*Renal* — Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of ██████████. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS (*see* *Renal under* **Single-Agent Use and under Post-marketing experience in** **ADVERSE REACTIONS** section).

*Hepatic* — Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving ██████████ alone or in combination with other potentially hepatotoxic drugs (*see* *Hepatic under* **Single-Agent Use and under Post-marketing experience in** **ADVERSE REACTIONS** section).

**Pregnancy** — Pregnancy Category D. [REDACTED] can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m<sup>2</sup> basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m<sup>2</sup> basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of [REDACTED] in pregnant women. If [REDACTED] is used during pregnancy, or if the patient becomes pregnant while taking [REDACTED], the patient should be apprised of the potential hazard to the fetus.

### PRECAUTIONS

**General** — Patients receiving therapy with Gemcitabine should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

**Laboratory Tests** — Patients receiving Gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected (*see* **DOSAGE AND ADMINISTRATION**).

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter (*see* **WARNINGS**).

**Carcinogenesis, Mutagenesis, Impairment of Fertility** — Long-term animal studies to evaluate the carcinogenic potential of [REDACTED] have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m<sup>2</sup> basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the human dose on a mg/m<sup>2</sup> basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m<sup>2</sup> basis).

**Pregnancy** — Category D. *See* **WARNINGS**.

**Nursing Mothers** — It is not known whether [REDACTED] or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from [REDACTED] in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

**Elderly Patients** — [REDACTED] clearance is affected by age (*see* **CLINICAL PHARMACOLOGY**). There is no evidence, however, that unusual dose adjustments (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. *Grade 3/4* thrombocytopenia was more common in the elderly.

*Gender* — [REDACTED] clearance is affected by gender (see **CLINICAL PHARMACOLOGY**). In the single-agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments (i.e., other than those already recommended in the **DOSAGE AND ADMINISTRATION** section) are necessary in women. In general, in single-agent studies of [REDACTED], adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

*Pediatric Patients* — The effectiveness of [REDACTED] in pediatric patients has not been demonstrated. [REDACTED] was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m<sup>2</sup>/min for 360 minutes three times weekly followed by a one-week rest period. [REDACTED] was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m<sup>2</sup>/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

*Patients with Renal or Hepatic Impairment* — [REDACTED] should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. [REDACTED] has not been studied in patients with significant renal or hepatic impairment.

*Drug Interactions* — No specific drug interaction studies have been conducted. For information on the pharmacokinetics of [REDACTED] and cisplatin in combination, see *Drug Interactions under CLINICAL PHARMACOLOGY* section.

*Radiation Therapy* — Safe and effective regimens for the administration of [REDACTED] with therapeutic doses of radiation have not yet been determined.

## ADVERSE REACTIONS

[REDACTED] has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs.

**Single-Agent Use:** Myelosuppression is the principal dose-limiting toxicity with [REDACTED] therapy. Dosage adjustments for hematologic toxicity are frequently needed and are described in the **DOSAGE AND ADMINISTRATION** section.

The data in Table 5 are based on 979 patients receiving [REDACTED] as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The [REDACTED] starting doses ranged from 800 to 1250 mg/m<sup>2</sup>. Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO Grade 3 or 4) adverse events were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of [REDACTED] therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

All WHO-graded laboratory events are listed in Table 5, regardless of causality. Non-laboratory adverse events listed in Table 5 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and Infection categories. Table

6 presents the data from the comparative trial of [REDACTED] and 5-FU in pancreatic cancer for the same adverse events as those in Table 5, regardless of incidence.

**Table 5: Selected WHO-Graded Adverse Events in Patients Receiving Single-Agent Gemcitabine  
WHO Grades (% incidence)**

	All Patients <sup>a</sup>			Pancreatic Cancer Patients <sup>b</sup>			Discontinuations (%) <sup>c</sup>
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	
<b>Laboratory<sup>d</sup></b>							
<b>Hematologic</b>							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
<b>Hepatic</b>							<1
ALT	68	8	2	72	10	1	
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
<b>Renal</b>							<1
Proteinuria	45	<1	0	32	<1	0	
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
<b>Non-laboratory<sup>e</sup></b>							
Nausea and Vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

Grade based on criteria from the World Health Organization (WHO).

<sup>a</sup> N=699-974; all patients with laboratory or non-laboratory data.

<sup>b</sup> N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.

<sup>c</sup> N=979.

<sup>d</sup> Regardless of causality.

<sup>e</sup> Table includes non-laboratory data with incidence for all patients  $\geq 10\%$ . For approximately 60% of the patients, non-laboratory events were graded only if assessed to be possibly drug-related.

**Table 6: Selected WHO-Graded Adverse Events from Comparative Trial of Gemcitabine and 5-FU in Pancreatic Cancer**  
**WHO Grades (% incidence)**

	Gemcitabine <sup>a</sup>			5-FU <sup>b</sup>		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>c</sup></b>						
<b>Hematologic</b>						
Anemia	65	7	3	45	0	0
Leukopenia	71	10	0	15	2	0
Neutropenia	62	19	7	18	2	3
Thrombocytopenia	47	10	0	15	2	0
<b>Hepatic</b>						
ALT	72	8	2	38	0	0
AST	72	10	2	52	2	0
Alkaline Phosphatase	71	16	0	64	10	3
Bilirubin	16	2	2	25	6	3
<b>Renal</b>						
Proteinuria	10	0	0	2	0	0
Hematuria	13	0	0	0	0	0
BUN	8	0	0	10	0	0
Creatinine	2	0	0	0	0	0
<b>Non-laboratory<sup>d</sup></b>						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

Grade based on criteria from the World Health Organization (WHO).

<sup>a</sup> N=58-63, all Gemcitabine patients with laboratory or non-laboratory data.

<sup>b</sup> N=61-63, all 5-FU patients with laboratory or non-laboratory data.

<sup>c</sup> Regardless of causality.

<sup>d</sup> Non-laboratory events were graded only if assessed to be possibly drug-related.

**Hematologic** – In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with [REDACTED], but <1% of patients discontinued therapy for either anemia, leucopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during [REDACTED] therapy and dosage modified or suspended according to the degree of hematologic toxicity (*see* **DOSAGE AND ADMINISTRATION**).

*Gastrointestinal* — Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

*Hepatic* — In clinical trials, [REDACTED] was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to [REDACTED] or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving [REDACTED] alone or in combination with other potentially hepatotoxic drugs (*see Hepatic under Post-marketing experience*).

*Renal* — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving [REDACTED] in clinical trials. Four patients developed HUS on [REDACTED] therapy, two immediately post-therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). [REDACTED] therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (*see Renal under Post-marketing experience*).

*Fever* — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that [REDACTED] may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

*Rash* — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

*Pulmonary* --- In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with [REDACTED] therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of [REDACTED] (*see Pulmonary under Post-marketing experience*). The etiology of these effects is unknown. If such effects develop, [REDACTED] should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

*Edema* — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

*Flu-like Symptoms* — “Flu syndrome” was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

*Infection* — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

*Alopecia* — Hair loss, usually minimal, was reported by 15% of patients.

**Neurotoxicity** — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

**Extravasation** — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. [REDACTED] is not a vesicant.

**Allergic** — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. [REDACTED] should not be administered to patients with a known hypersensitivity to this drug (see **CONTRAINDICATION**).

**Cardiovascular** — During clinical trials, 2% of patients discontinued therapy with [REDACTED] due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease (see *Cardiovascular under Post-marketing experience*).

**Combination Use in Non-Small Cell Lung Cancer:** In the [REDACTED] plus cisplatin vs. cisplatin study, dose adjustments occurred with 35% of [REDACTED] injections and 17% of cisplatin injections on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations for possibly drug-related adverse events occurred in 15% of patients on the combination arm and 8% of patients on the cisplatin arm. With a median of 4 cycles of [REDACTED] plus cisplatin treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly treatment-related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse events.

In the [REDACTED] plus cisplatin vs. etoposide plus cisplatin study, dose adjustments occurred with 20% of [REDACTED] injections and 16% of cisplatin injections in the [REDACTED] plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of [REDACTED] plus cisplatin treatment, 15 of 69 patients (22%) experienced 15 hospitalizations due to possibly treatment-related adverse events. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%) experienced 22 hospitalizations due to possibly treatment-related adverse events. In patients who completed more than one cycle, dose adjustments were reported in 81% of the [REDACTED] plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse events occurred in 14% of patients on the [REDACTED] plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with [REDACTED] plus cisplatin treatment (~90%) compared to that with the [REDACTED] monotherapy (~60%). With combination therapy, [REDACTED] dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

Table 7 presents the safety data from the [REDACTED] plus cisplatin vs. cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and 1 case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the [REDACTED] plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in 4 possibly treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients on the [REDACTED] plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were rare. Red blood cell transfusions were required in 39% of the patients on the [REDACTED] plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued [REDACTED] plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred slightly more often with [REDACTED] plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent [REDACTED], a lower incidence of nausea and vomiting (58% to 69%) was reported. Renal function abnormalities, hypomagnesaemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with [REDACTED] plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with [REDACTED] plus cisplatin compared to one (<1%) Grade 3 dysrhythmia reported with cisplatin therapy. Hypomagnesaemia and hypokalemia were associated with one Grade 4 arrhythmia on the [REDACTED] plus cisplatin combination arm.

Table 8 presents data from the randomized study of [REDACTED] plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in Table 6. One death (1.5%) was reported on the [REDACTED] plus cisplatin arm due to febrile neutropenia associated with renal failure, which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the [REDACTED] plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% vs. 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the [REDACTED] plus cisplatin arm. RBC transfusions were given to 29% of the patients who received [REDACTED] plus cisplatin vs. 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received [REDACTED] plus cisplatin vs. 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the [REDACTED] plus cisplatin arm. On the [REDACTED] plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of [REDACTED] as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the [REDACTED] plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the [REDACTED] plus cisplatin arm reported edema compared to 1 patient (2%) on the etoposide plus cisplatin arm.

**Table 7: Selected CTC-Graded Adverse Events from Comparative Trial of Gemcitabine plus Cisplatin versus Single-Agent Cisplatin in NSCLC**  
**CTC Grades (% incidence)**

	Gemcitabine plus Cisplatin <sup>a</sup>			Cisplatin <sup>b</sup>		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>c</sup></b>						
<b>Hematologic</b>						
Anemia	89	22	3	67	6	1
RBC Transfusions <sup>d</sup>	39			13		
Leukopenia	82	35	11	25	2	1
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions <sup>d</sup>	21			<1		
Lymphocytes	75	25	18	51	12	5
<b>Hepatic</b>						
Transaminase	22	2	1	10	1	0
Alkaline Phosphatase	19	1	0	13	0	0
<b>Renal</b>						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
<b>Other Laboratory</b>						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
<b>Non-laboratory<sup>e</sup></b>						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
Constipation	28	3	0	21	0	0
Neuro Hearing	25	6	0	21	6	0
Diarrhea	24	2	2	13	0	0
Neuro Sensory	23	1	0	18	1	0
Infection	18	3	2	12	1	0
Fever	16	0	0	5	0	0
Neuro Cortical	16	3	1	9	1	0
Neuro Mood	16	1	0	10	1	0
Local	15	0	0	6	0	0
Neuro Headache	14	0	0	7	0	0
Stomatitis	14	1	0	5	0	0
Hemorrhage	14	1	0	4	0	0
Dyspnea	12	4	3	11	3	2
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse events with incidence  $\geq 10\%$  in either arm.  
(a) N=217-233; all Gemcitabine plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine at 1000 mg/m<sup>2</sup> on Days 1, 8, and 15 and cisplatin at 100 mg/m<sup>2</sup> on Day 1 every 28 days.  
(b) N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m<sup>2</sup> on Day 1 every 28 days.  
(c) Regardless of causality.  
(d) Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.  
(e) Non-laboratory events were graded only if assessed to be possibly drug-related.

**Table 8: Selected WHO-Graded Adverse Events from Comparative Trial of Gemcitabine plus Cisplatin versus Etoposide plus Cisplatin in NSCLC**

	WHO Grades (% incidence)			WHO Grades (% incidence)		
	Gemcitabine plus Cisplatin <sup>a</sup>			Etoposide plus Cisplatin <sup>b</sup>		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>c</sup></b>						
<b>Hematologic</b>						
Anemia	88	22	0	77	13	2
RBC Transfusions <sup>d</sup>	29			21		
Leukopenia	86	26	3	87	36	7
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions <sup>d</sup>	3			8		
<b>Hepatic</b>						
ALT	6	0	0	12	0	0
AST	3	0	0	11	0	0
Alkaline Phosphatase	16	0	0	11	0	0
Bilirubin	0	0	0	0	0	0
<b>Renal</b>						
Proteinuria	12	0	0	5	0	0
Hematuria	22	0	0	10	0	0
BUN	6	0	0	4	0	0
Creatinine	2	0	0	2	0	0
<b>Non-laboratory<sup>e,f</sup></b>						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Constipation	17	0	0	15	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0

Grade based on criteria from the World Health Organization (WHO).

(a) N=67-69; all Gemcitabine plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine at 1250 mg/m<sup>2</sup> on

Days 1 and 8 and cisplatin at 100 mg/m<sup>2</sup> on Day 1 every 21 days.

(b) N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m<sup>2</sup> on Day 1 and 14, etoposide at 100 mg/m<sup>2</sup> on Days 1, 2, and 3 every 21 days.

(c) Regardless of causality.

(d) Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.

(e) Non-laboratory events were graded only if assessed to be possibly drug-related.

(f) Pain data were not collected.

**Combination Use in Breast Cancer:** In the [REDACTED] plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of [REDACTED] injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of [REDACTED] doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7%) on the [REDACTED] plus paclitaxel arm and 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug-related, one on each arm.

Table 9 presents the safety data occurrences of  $\geq 0\%$  (all grades) from the [REDACTED] plus paclitaxel versus paclitaxel study in breast cancer.

**Table 9: Adverse Events from Comparative Trial of Gemcitabine plus Paclitaxel Versus Single-Agent Paclitaxel in Breast Cancer<sup>a</sup>**  
CTC Grades (% incidence)

	Gemcitabine plus Paclitaxel (N=262)			Paclitaxel (N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>b</sup></b>						
<b>Hematologic</b>						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Leukopenia	21	10	1	12	2	0
<b>Hepatobiliary</b>						
ALT	18	5	<1	6	<1	0
AST	16	2	0	5	<1	0
<b>Non-laboratory<sup>c</sup></b>						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Myalgia	33	4	0	33	3	<1
Vomiting	29	2	0	15	2	0
Arthralgia	24	3	0	22	2	<1
Diarrhea	20	3	0	13	2	0
Anorexia	17	0	0	12	<1	0
Neuropathy-motor	15	2	<1	10	<1	0
Stomatitis/pharyngitis	13	1	<1	8	<1	0
Fever	13	<1	0	3	0	0
Constipation	11	<1	0	12	0	0
Bone pain	11	2	0	10	<1	0
Pain-other	11	<1	0	8	<1	0
Rash/desquamation	11	<1	<1	5	0	0

<sup>a</sup> Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades  $\geq 10\%$ ).

<sup>b</sup> Regardless of causality.

<sup>c</sup> Non-laboratory events were graded only if assessed to be possibly drug-related.

The following are the clinically relevant adverse events that occurred in  $>1\%$  and  $<10\%$  (all grades) of patients on either arm. In parentheses are the incidences of Grades 3 and 4 adverse events ([REDACTED] plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0%), and allergic reaction / hypersensitivity (0 versus 0.8%).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

**Post-Marketing Experience:** The following adverse events have been identified during post-approval use of [REDACTED]. These events have occurred after [REDACTED] single-agent use and [REDACTED] in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to [REDACTED].

*Cardiovascular* — Congestive heart failure and myocardial infarction have been reported very rarely with the use of [REDACTED]. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

*Vascular Disorders* — Vascular toxicity reported with [REDACTED] includes clinical signs of vasculitis, which has been reported very rarely. Gangrene has also been reported very rarely.

*Skin* — Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported.

*Hepatic* — Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving [REDACTED] alone, or in combination with other potentially hepatotoxic drugs.

*Pulmonary* — Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of [REDACTED] administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last [REDACTED] dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

*Renal* — Hemolytic-Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of [REDACTED]. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

### **OVERDOSAGE**

There is no known antidote for overdoses of [REDACTED]. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m<sup>2</sup> was administered by I.V. infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

## DOSAGE AND ADMINISTRATION

is for intravenous use only.

### Adults

#### Single-Agent Use:

**Pancreatic Cancer** - should be administered by intravenous infusion at a dose of 1000 mg/m<sup>2</sup> over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

**Dose Modifications** - Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient (*see WARNINGS*). Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles (*see Human Pharmacokinetics under CLINICAL PHARMACOLOGY and PRECAUTIONS*).

Patients receiving should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 10.

**Table 10: Dosage Reduction Guidelines**

Absolute granulocyte count (x 10 <sup>6</sup> /L)		Platelet count (x 10 <sup>6</sup> /L)	% of full dose
≥1000	and	≥100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10<sup>6</sup>/L and 100,000 x 10<sup>6</sup>/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10<sup>6</sup>/L and 100,000 x 10<sup>6</sup>/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

### Combination Use:

*Non-Small Cell Lung Cancer* - Two schedules have been investigated and the optimum schedule has not been determined (see **CLINICAL STUDIES**). With the 4-week schedule, [REDACTED] should be administered intravenously at 1000 mg/m<sup>2</sup> over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m<sup>2</sup> on Day 1 after the infusion of [REDACTED]. With the 3-week schedule, [REDACTED] should be administered intravenously at 1250 mg/m<sup>2</sup> over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m<sup>2</sup> should be administered intravenously after the infusion of [REDACTED] on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

*Dose Modifications* - Dosage adjustments for hematologic toxicity may be required for [REDACTED] and for cisplatin. [REDACTED] dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving [REDACTED] should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 10. For cisplatin dosage adjustment, see manufacturer's prescribing information.

In general, for severe (Grades 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with [REDACTED] plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grades 3/4 serum creatinine toxicity for [REDACTED] plus cisplatin was 5% versus 2% for cisplatin alone).

*Breast Cancer* — [REDACTED] should be administered intravenously at a dose of 1250 mg/m<sup>2</sup> over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m<sup>2</sup> on Day 1 as a 3-hour intravenous infusion before [REDACTED] administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count  $\geq 500 \times 10^6/L$  and a platelet count  $\geq 100,000 \times 10^6/L$  prior to each cycle.

*Dose Modifications* — [REDACTED] dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, [REDACTED] dosage should be modified according to the guidelines in Table 11.

**Table 11: Day 8 Dosage Reduction Guidelines for Gemcitabine in Combination with Paclitaxel**

Absolute granulocyte count ( $\times 10^6/L$ )		Platelet count ( $\times 10^6/L$ )	% of full dose
$\geq 1200$	and	$>75,000$	100
1000-1199	or	50,000-75,000	75
700-999	and	$\geq 50,000$	50
$<700$	or	$<50,000$	Hold

In general, for severe (Grades 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with [REDACTED] should be held or decreased by 50% depending on the judgment of the treating physician. For paclitaxel dosage adjustment, see manufacturer's prescribing information.

██████████ may be administered on an outpatient basis.

*Instructions for Use/Handling:* The recommended diluent for reconstitution of ██████████ is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for ██████████ upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial, 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial, ██████████. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL, which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial, 1.3 mL for the 1-g vial ██████████). The total volume upon reconstitution will be 5.26 mL, 26.3 mL ██████████, respectively. Complete withdrawal of the vial contents will provide 200 mg, 1 g, ██████████ of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

Reconstituted ██████████ is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, ██████████ solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Discard unused portion. Solutions of reconstituted ██████████ should not be refrigerated, as crystallization may occur.

The compatibility of ██████████ with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Unopened vials of ██████████ are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Caution should be exercised in handling and preparing ██████████ solutions. The use of gloves is recommended. If ██████████ solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water, or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.<sup>1-8</sup> There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

## HOW SUPPLIED

### Vials:

██████████

Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

### REFERENCES

1. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH publication No. 83-2621. U.S. Government Printing Office, Washington, DC 20402.
2. Council on Scientific Affairs: Guidelines for handling parenteral antineoplastics. *JAMA* 1985;253:1590.
3. National Study Commission on Cytotoxic Exposure — Recommendations for handling cytotoxic agents, 1987. Available from Louis P. Jeffrey, ScD, Director of Pharmacy Services, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02902.
4. Clinical Oncological Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Aust* 1983;1:426.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA* 1983;33(Sept/Oct):258.
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8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburg, PA: Oncology Nursing Society; 1999:32-41.

**Name of Manufacturer and/or Distributor  
City, State and Zip Code**

