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Approval Package for:

APPLICATION NUMBER:

20-509/S033

Trade Name: Gemzar

Generic Name: Gemcitabine, HCL

Sponsor: Eli Lilly and Co

Approval Date: April 26, 2005

Indications:

Breast Cancer
Non-Small Cell Lung Cancer
Pancreatic Cancer

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APPLICATION NUMBER:

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APPLICATION NUMBER:

20-509/S033

APPROVAL LETTER

.ENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

-509/S-033

. Lilly & Company
ttention: Colleen Mockbee, R.Ph.
Manager, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Mockbee:

Please refer to your supplemental new drug application dated October 26, 2004, received October 27, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar® (gemcitabine HCl) for Injection.

We acknowledge receipt of your submissions dated January 11 and 17, 2005.

This supplemental new drug application provides for revisions to the *Pediatric Patients* subsection of the PRECAUTIONS section of the package insert to reflect data from pediatric studies conducted pursuant to the January 9, 2001 Pediatric Written Request.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). In addition, the FPL should include the revisions of supplement 031, which was approved on March 24, 2005, and supplement 032, which was approved on April 20, 2005.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved supplement NDA 20-509/S-031, S-032, and S-033**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
4/26/05 11:54:25 AM

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APPLICATION NUMBER:

20-509/S033

LABELING

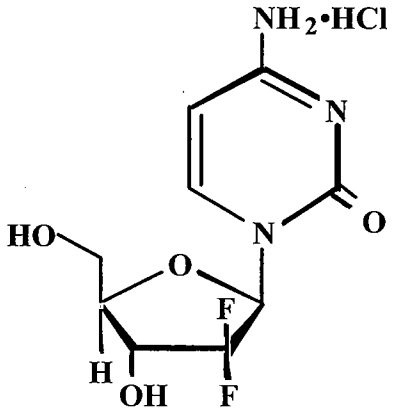
B1.0 NL 4063 AMP

GEMZAR®
(GEMCITABINE HCl)
FOR INJECTION

DESCRIPTION

Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-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 Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, 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-potentiation). 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^2/30 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 Gemzar dose varied from 500 to 3600 mg/m^2.

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 Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] 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

[a] 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 results 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^2 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^2, 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 Gemzar (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 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 Gemzar in combination with paclitaxel for treatment of breast cancer patients who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Gemzar 1250 mg/m^2 was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m^2 administered prior to Gemzar on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle as the control arm.

The addition of Gemzar 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 Gemzar based on an interim survival analysis.

Table 2: Gemzar Plus Paclitaxel Versus Paclitaxel in Breast Cancer

	Gemzar/Paclitaxel	Paclitaxel	
Number of patients	267	262	
Median age, years Range	53 26 to 83	52 26 to 75	
Metastatic disease	97.0%	96.9%	
Baseline KPS[a] ≥90	70.4%	74.4%	
Number of tumor sites 1-2 ≥3	 56.6% 43.4%	 58.8% 41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	

Time to Documented Disease Progression[b] Median (95%, C.I.), months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)	p<0.0001
Hazard Ratio (95% C.I.)	0.650 (0.524, 0.805)		p<0.0001
Overall Response Rate[b] (95%, C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)	p<0.0001

[a] Karnofsky Performance Status.

[b] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

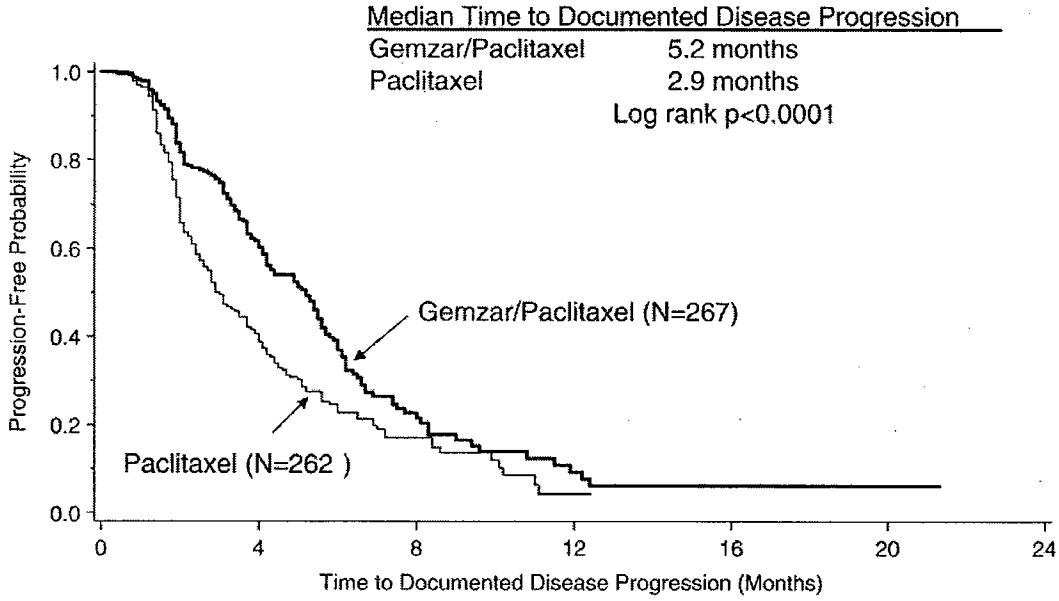


Figure 1: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemzar plus Paclitaxel versus Paclitaxel Breast Cancer Study (N=529).

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

Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemzar 1000 mg/m^2 was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m^2 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 Gemzar plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the Gemzar 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 Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.009, two-sided). The objective response rate on the Gemzar 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.

Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to etoposide 100 mg/m^2 I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m^2 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 Gemzar plus cisplatin arm

versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemzar 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 Gemzar 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 Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm and the comparator arm.

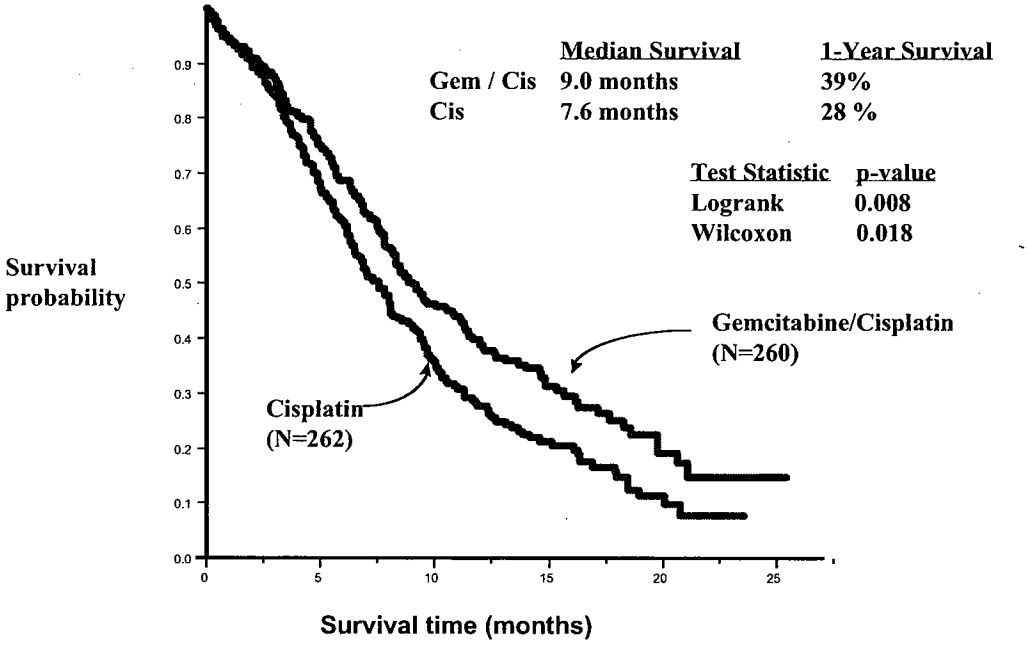


Figure 2: Kaplan-Meier Survival Curve in Gemzar plus Cisplatin versus Cisplatin NSCLC Study (N=522).

147

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

Trial	28-day Schedule[a]			21-day Schedule[b]		
Treatment Arm	Gemzar/ Cisplatin	Cisplatin		Gemzar/ 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[c] 70 to 80	41%	44%		45%	52%	
Baseline KPS[c] 90 to 100	57%	55%		55%	49%	

148

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[d]	33%	14%	p=0.01[d]

149 [a] 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on
150 Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.
151 [b] 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on
152 Day 1
153 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and I.V. etoposide
154 100 mg/m^2 on Days 1, 2, and 3 every 21 days.
155 [c] Karnofsky Performance Status.
156 [d] p-value for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial
157 proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.
158 N/A Not applicable.
159

160 *Pancreatic Cancer* — Data from 2 clinical trials evaluated the use of Gemzar in patients with
161 locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to
162 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial
163 studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a
164 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered
165 intravenously at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until
166 toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar.
167 Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every
168 4 weeks.
169 The primary efficacy parameter in these studies was "clinical benefit response," which is a
170 measure of clinical improvement based on analgesic consumption, pain intensity, performance
171 status, and weight change. Definitions for improvement in these variables were formulated
172 prospectively during the design of the 2 trials. A patient was considered a clinical benefit
173 responder if either:

i) the patient showed a ≥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 (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation.

The first study was a multi-center (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemzar 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^2 for 30 minutes. The results from this randomized trial are shown in Table 4. Patients treated with Gemzar 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: Gemzar Versus 5-FU in Pancreatic Cancer

	Gemzar	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[a] ≤70	69.8%	68.3%	

Clinical benefit response	22.2% (N[c]=14)	4.8% (N=3)	p=0.004
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability[b]	(N=30) 46%	(N=19) 29%	
9-month probability[b]	(N=14) 24%	(N=4) 5%	
1-year probability[b]	(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	

[a] Karnofsky Performance Status.
[b] Kaplan-Meier estimates.
[c] 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 Gemzar and 3 patients treated with 5-FU. One patient on the Gemzar arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemzar 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 Gemzar 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.

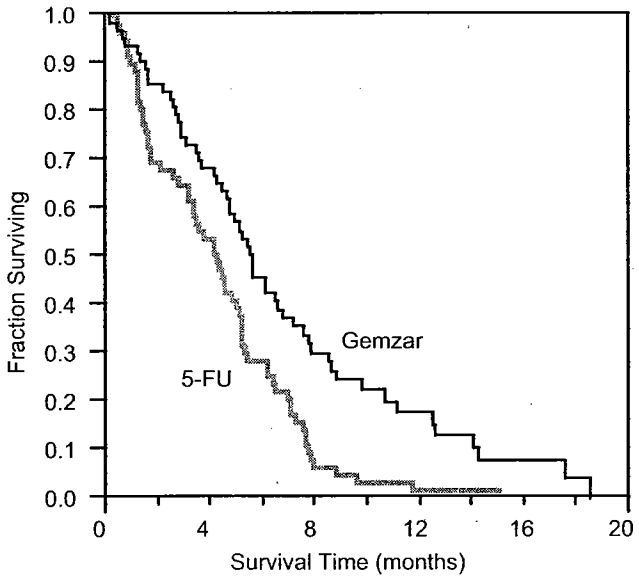


Figure 3: Kaplan-Meier Survival Curve.

The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar 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 Gemzar 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 Gemzar 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^2. 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^2 (30-minute infusion) and 150 mg/m^2 (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^2 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 Gemzar is administered more frequently than once weekly or with infusions longer than 60 minutes (*see* **WARNINGS**).

INDICATIONS AND USAGE

Therapeutic Indications

Breast Cancer — Gemzar 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 — Gemzar 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 — Gemzar 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. Gemzar is indicated for patients previously treated with 5-FU.

CONTRAINDICATION

Gemzar 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 have been shown to increase toxicity (*see* **CLINICAL STUDIES**).

Hematology — Gemzar can suppress bone marrow function as manifested by leukopenia, 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 Gemzar. In cases of severe lung toxicity, Gemzar 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 Gemzar. 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 Gemzar 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. Gemzar 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^2 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^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General — Patients receiving therapy with Gemzar 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 Gemzar 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 Gemzar 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^2 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^2 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^2 basis).

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

Nursing Mothers — It is not known whether Gemzar 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 Gemzar 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 — Gemzar 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 — Gemzar 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 Gemzar, 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 Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one week rest period. Gemzar 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^2/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 — Gemzar should be used with caution in patients with preexisting renal impairment or hepatic insufficiency. Gemzar 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 Gemzar and cisplatin in combination, *see Drug Interactions under* **CLINICAL PHARMACOLOGY** section.

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

ADVERSE REACTIONS

Gemzar 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 Gemzar 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 Gemzar as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar starting doses ranged from 800 to 1250 mg/m^2. 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 Gemzar 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 Gemzar 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 Gemzar
WHO Grades (% incidence)

	All Patients[a]			Pancreatic Cancer Patients[b]			Discontinuations (%)[c]
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory[d]							
Hematologic							
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
Hepatic							<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	
Renal							<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	
Non-laboratory[e]							
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).

[a] N=699-974; all patients with laboratory or non-laboratory data.

[b] N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data.

[c] N=979.

[d] Regardless of causality.

[e] Table includes non-laboratory data with incidence for all patients ≥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 Gemzar and 5-FU in Pancreatic Cancer
WHO Grades (% incidence)

	Gemzar[a]			5-FU[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
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
Hepatic						
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
Renal						
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
Non-laboratory[d]						
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).
[a] N=58-63; all Gemzar patients with laboratory or non-laboratory data.
[b] N=61-63; all 5-FU patients with laboratory or non-laboratory data.
[c] Regardless of causality.
[d] 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 Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, 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 Gemzar 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, Gemzar 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 Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar 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 Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 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). Gemzar 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 Gemzar 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 Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar (*see Pulmonary under* **Post-marketing experience**). The etiology of these effects is unknown. If such effects develop, Gemzar 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. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar 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 Gemzar 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 Gemzar plus cisplatin vs. cisplatin study, dose adjustments occurred with 35% of Gemzar 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 Gemzar 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 Gemzar plus cisplatin vs. etoposide plus cisplatin study, dose adjustments occurred with 20% of Gemzar injections and 16% of cisplatin injections in the Gemzar 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 Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemzar plus cisplatin treatment (~90%) compared to that with the Gemzar monotherapy (~60%). With combination therapy Gemzar 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 Gemzar 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 Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued Gemzar plus cisplatin use.

Nausea and vomiting despite the use of antiemetics occurred slightly more often with Gemzar plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent

Gemzar, a lower incidence of nausea and vomiting (58% to 69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with Gemzar plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with Gemzar plus cisplatin compared to one (<1%) Grade 3 dysrrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the Gemzar plus cisplatin combination arm.

Table 8 presents data from the randomized study of Gemzar 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 Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm. RBC transfusions were given to 29% of the patients who received Gemzar plus cisplatin vs. 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received Gemzar plus cisplatin vs. 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the Gemzar plus cisplatin arm. On the Gemzar 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 Gemzar 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 Gemzar plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemzar 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 Gemzar plus Cisplatin versus Single-Agent Cisplatin in NSCLC

CTC Grades (% incidence)

	Gemzar plus Cisplatin[a]			**Cisplatin[b]**		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion[d]	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[d]	21			<1		
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22	2	1	10	1	0
Alkaline Phosphatase	19	1	0	13	0	0
Renal						

Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[e]						
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 ≥10% in either arm.

[a] N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[b] N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 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 Gemzar plus Cisplatin versus Etoposide plus Cisplatin in NSCLC

WHO Grades (% incidence)

	Gemzar plus Cisplatin[a]			Etoposide plus Cisplatin[b]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[c]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[d]	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[d]	3			8		
Hepatic						
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
Renal						
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
Non-laboratory[e,f]						
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 Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 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^2 on Day 1 and I.V. etoposide at 100 mg/m^2 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 Gemzar plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar 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 Gemzar 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 ≥10% (all grades) from the Gemzar plus paclitaxel versus paclitaxel study in breast cancer.

Table 9: Adverse Events from Comparative Trial of Gemzar plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer[a]

CTC Grades (% incidence)

	Gemzar plus Paclitaxel (N=262)			Paclitaxel (N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
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
Hepatobiliary						
ALT	18	5	<1	6	<1	0
AST	16	2	0	5	<1	0
Non-laboratory[c]						
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

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%).
[b] Regardless of causality.
[c] 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 Grade 3 and 4 adverse events (Gemzar 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 Gemzar. These events have occurred after Gemzar single-agent use and Gemzar 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 Gemzar.

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

Vascular Disorders — Vascular toxicity reported with Gemzar 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 Gemzar 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 Gemzar administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar 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 Gemzar. 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 Gemzar. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 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

Gemzar is for intravenous use only.

Adults

Single-Agent Use:

Pancreatic Cancer — Gemzar should be administered by intravenous infusion at a dose of 1000 mg/m^2 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 Gemzar 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 10^6/L)		Platelet count (x 10^6/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. Gemzar should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with Gemzar 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 10^6/L and 100,000 x 10^6/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemzar 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 10^6/L and 100,000 x 10^6/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, Gemzar should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemzar on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications — Dosage adjustments for hematologic toxicity may be required for Gemzar and for cisplatin. Gemzar dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemzar 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 (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemzar 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 (Grade 3/4 serum creatinine toxicity for Gemzar plus cisplatin was 5% versus 2% for cisplatin alone).

Breast Cancer — Gemzar should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

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

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

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

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

Gemzar may be administered on an outpatient basis.

Instructions for Use/Handling — The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar 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 or 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 or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 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 Gemzar 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, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [*See* USP]. Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

The compatibility of Gemzar 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 Gemzar 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].

Caution should be exercised in handling and preparing Gemzar solutions. The use of gloves is recommended. If Gemzar 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.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Vials:

200 mg white, lyophilized powder in a 10-mL size sterile single use vial (No. 7501)
NDC 0002-7501-01

1 g white, lyophilized powder in a 50-mL size sterile single use vial (No. 7502)
NDC 0002-7502-01

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. US 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.
6. American Society of Hospital Pharmacists: Technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm* 1990;47:1033.
7. Controlling Occupational Exposure to Hazardous Drugs, OSHA Work Practice Guidelines. *Am J Health-Sys Pharm* 1996;53:1669-1685.
8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburg, PA: Oncology Nursing Society; 1999:32-41.

Literature revised Month,dd,yyyy

Eli Lilly and Company
Indianapolis, IN 46285, USA

B1.0 NL 4063 AMP PRINTED IN USA

22 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509/S033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 20-509 SUPPL # 033

Trade Name:Gemzar® for Injection Generic Name:gemcitabine HCl

Applicant Name: Eli Lilly and Company HFD# 150

Approval Date: April 26, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / **X** / NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) - SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / **X** / NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Pediatric Exclusivity determination - No efficacy claim is made. The applicant proposed to include the study information in the label. The clinical review team accepted the applicant's proposed labeling language under the PRECAUTIONS section, Pediatric Patients subsection.

d) Did the applicant request exclusivity?

YES / **X** / NO /___/

If the answer to (d) is "yes," how many years of exclusivity

did the applicant request?

6 months

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / **X** / NO /___/

If the answer to the above question is YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

YES

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO / **X** /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / **X** / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-509 **Gemzar**

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO / **X** /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA#. _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / **X** / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / **X** / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?
This is a Pediatric Supplement for an approved product which has been granted 6 months exclusivity effective January 27, 2005 (see Pediatric Exclusivity Determination Checklist in DFS). The applicant met all of the requirements of the Pediatric Written Request. No efficacy claim is made and no labeling changes have occurred in this regard. The only labeling revision is in the PRECAUTIONS, Pediatric Patients subsection, which included the pediatric study description.

YES /___/ NO / **X** /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / **X** /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The applicant submitted results from 2 studies (listed below) to fulfill the Agency's January 9, 2001 Pediatric Written Request letter.

Phase 1 study: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.
Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients with each refractory ALL and AML or relapsed tumor(s). Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / **X** /

Investigation #2 YES /___/ NO / **X** /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / **X** /

Investigation #2 YES /___/ NO / **X** /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

The applicant submitted results from 2 studies (listed below) to fulfill the Agency's January 9, 2001 Pediatric Written Request letter.

Phase 1 study: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.

Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients with each refractory ALL and AML or relapsed tumor(s). Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 29,653 YES / X / ! NO /___/ Explain: _____

Investigation #2

IND # 29,653 YES / X / ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

_____

_____ _____
Patty Garvey, R.Ph. Date
Regulatory Project Manager

_____ _____
Richard Pazdur, M.D. Date
Signature of Division Director

Form OGD-011347 Revised 05/10/2004

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/s/

Richard Pazdur
4/26/05 12:00:01 PM

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 1/9/01. Application Written Request was made to: NDA# 20-509

Timeframe Noted in Written Request for Submission of Studies 11/1/2005.

NDA# 20-509 Supplement #033 Choose one: SE8

Sponsor Eli Lilly and Company

Generic Name gemcitabine HCl Trade Name Gemzar®

Strength Dosage Form/Route Injection/Intravenous

Date of Submission of Reports of Studies 10/26/2004.

Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 1/24/2005.

Was a formal Written Request made for the pediatric studies submitted?	Y _X__	N ___
Were the studies submitted after the Written Request?	Y _X__	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y _X__	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y _X__	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y _X__	N ___
Did the studies fairly respond to the Written Request?	Y _X__	N ___

SIGNED Martin H. Cheng MD (Reviewing Medical Officer) DATE 1/5/05

SIGNED DIV. DIR. DATE 1/5/05

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-509	4808614	May 15, 2010
20-509	5464826	Nov 07, 2012
20-509	I-428	May 19, 2004

SIGNED DATE 1/27/05

Revised: 11/30/2001

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/s/

Debbie Avant
1/28/05 04:03:07 PM

CERTIFICATION

NDA Application No.: **20-509**

Drug Name: **Gemzar**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Debasish F. Roychowdhury, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Norma Ascroft, Pharm.D.

Title: Manager, U.S. Regulatory Affairs-Oncology

Date: October 26, 2004

REGULATORY PROJECT MANAGER REVIEW
ADDENDUM #1

NDA: 20-509 / S-033

Drug: Gemzar ® (Gemcitabine HCl) for Injection

Applicant: Eli Lilly and Company

Submission Dates: October 26, 2004 **Receipt Dates:** October 27, 2004

BACKGROUND:

The Division of Oncology Drug Products approved supplement 029 on May 19, 2004, which provided for the use of Gemzar® (gemcitabine HCl) for Injection in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

The Final Printed Labeling (FPL) was submitted for supplement 029 on July 26, 2004 and was acknowledged and retained on September 13, 2004.

A chemistry and manufacturing supplement, SCM-031 was submitted on October 7, 2004, and approved on March 24, 2005. Supplement 031 provided for a new manufacturing and packaging facility in France.

A labeling supplement, SLR-032 was submitted on October 19, 2004, approved on April 20, 2005. Supplement 032 provided for additional pharmacokinetics information regarding use of Gemzar with paclitaxel in breast cancer patients (CLINICAL PHARMACOLOGY; Drug Interactions) and minor editorial changes.

This supplement SE8-033 was submitted on October 26, 2004 and provided revisions to the PRECAUTIONS, *Pediatric Patients* section of the package insert. These revisions submitted reflect data from pediatric studies pursuant to the January 9, 2001 Pediatric Written Request. It does not include labeling revisions from supplement SCM-031 and SLR-032.

DOCUMENT REVIEWED:

I compared the October 26, 2004 supplement for S-033 to the FPL for supplement 029.

REVIEW:

The following paragraph "Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established" was deleted and replace with the following paragraph to the *Pediatric Patients* subsection of the PRECAUTIONS section.

> "The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with —— refractory leukemia ———————— and determined that the maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one week rest period. Gemzar 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^2/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."

The medical officer, Dr. Martin Cohen, reviewed the data submitted in this supplement and found that it supported the above additional paragraph.

ADDENDUM:

On April 13, 2005, the sponsor requested minor revisions to the above original proposed pediatric paragraph. They proposed ———————— from the paragraph because the ———————— however, none were actually enrolled.

> *Pediatric Patients* — The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with —— refractory leukemia ———————— and determined that the maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one week rest period. Gemzar 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^2/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.

The proposed deletions are acceptable to the clinical team.

RECOMMENDED REGULATORY ACTION:

This supplement 033 should be approved and FPL requested should also incorporate the revisions of supplement SCM-031, which was approved on March 24, 2005, and supplement SLR-032, which was approved on April 20, 2005.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Regulatory Project Manager

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff

Concurrence: M. Cohen/4-7-05
J. Johnson/4-7-05/4-13-05
D. Spillman for D. Pease/4-23-05

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/s/

Patricia Garvey
4/26/05 08:40:36 AM
CSO

Dotti Pease
4/26/05 10:48:20 AM
CSO

REGULATORY PROJECT MANAGER REVIEW

NDA: 20-509 / S-033

Drug: Gemzar ® (Gemcitabine HCl) for Injection

Applicant: Eli Lilly and Company

Submission Dates: October 26, 2004 **Receipt Dates:** October 27, 2004

BACKGROUND:

The Division of Oncology Drug Products approved supplement 029 on May 19, 2004, which provided for the use of Gemzar® (gemcitabine HCl) for Injection in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

The Final Printed Labeling (FPL) was submitted for supplement 029 on July 26, 2004 and was acknowledged and retained on September 13, 2004.

A chemistry and manufacturing supplement (SCM) was submitted for supplement 031 on October 7, 2004 and was approved on March 24, 2005. Supplement 031 provided for a new manufacturing and packaging facility in France.

This supplement 033 was submitted on October 26, 2004 and provided the pediatric study reports to fulfill the original Pediatric Written Request dated January 9, 2001. It does not include labeling revisions of SCM supplement 031 nor from pending SLR supplement 032.

DOCUMENT REVIEWED:

I compared the October 26, 2004 supplement for S-033 to the FPL for supplement 029.

REVIEW:

The following paragraph "Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established" was deleted and replace with the following paragraph to the *Pediatric Patients* subsection of the PRECAUTIONS section.

> "The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with —— refractory leukemia ———————— and determined that the maximum tolerated

dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one week rest period. Gemzar 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^2/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."

The medical officer, Dr. Martin Cohen, reviewed the data submitted in this supplement and found that it supported the above additional paragraph.

RECOMMENDED REGULATORY ACTION:

This supplement 033 should be approved and FPL requested which combines the revisions of supplement 033 and 031.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Regulatory Project Manager

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff

Concurrence: M. Cohen/4-7-05
J. Johnson/4-7-05

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/s/

Patricia Garvey
4/12/05 07:16:51 AM
CSO

Dotti Pease
4/12/05 08:12:43 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Colleen Mockbee, R.Ph. - Eli Lilly and Company	**From:**	Patty Garvey, R.Ph.
Fax:	317-276-1652	**Fax:**	(301) 594-0498
Phone:	317-277-0199	**Phone:**	(301) 594-5766
Pages (including cover):	1	**Date:**	January 6, 2005
Re:	NDA 20-509/S-033 Gemzar – submission dated 10-26-2004		

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ■ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Dear Colleen,

Please refer to NDA 20-509/s-033 Gemzar submission dated October 26, 2004 regarding your request for pediatric exclusivity. The Pediatric Exclusivity Board and the Division is currently reviewing your request and has the following questions.

1. [redacted]

2. Please explain why a full study report, similar to an NDA supplement, was not submitted for both the phase 1 and phase 2 acute leukemia studies. We did not receive individual patient data related to demographics, disease characteristics, prior therapy, prior transplant, treatment received, response and response duration.

We request your response by no later than January 13, 2005 since the determination for pediatric exclusivity due date is January 24, 2005.

Please contact me if you have any questions.

Sincerely,

Patty Garvey
Regulatory Project Manager
Division of Oncology Drug Products

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/s/

Patricia Garvey
1/6/05 04:58:24 PM
CSO

Pediatric Exclusivity Board

January 5, 2005

Pediatric Exclusivity Board Members Representatives	Review Division/ Office
Rosemary Roberts, OCTAP	Marty Cohen, HFD 150
Debbie Avant, Peds Team	Grant Williams, HFD-150
Edward Cox	Patty Garvey, HFD 150
Philip Sheridan	Bill Rodriquez, HFD-950
Dianne Murphy, OPT	
John Jenkins	
Aileen Ciampa, ORP	
Sonal Vaid - OCC	
Elizabeth Dickinson, OCC	
Dena Hixon	

Pediatric Exclusivity Determination for Gemzar (gemcitabine) Injectable – Lilly {NDA 20-509}

Initial Written Request:	Jan 09, 2001
Timeframe for submission of studies:	Nov 01, 2005
Date report of studies submitted:	Oct 26, 2004
Due Date for Pediatric Exclusivity Determination:	Jan 24, 2005

- The division noted that the sponsor submitted 2 studies:
  - A dose finding study, including pharmacokinetics and
  - Phase 2 or pilot study with at least 14 pediatric patients with each refractory ALL and AML or relapsed tumor(s).
- Indication to be studied: Refractory or relapsed leukemia
- The division noted several deviations from the Written Request:
  -
  - Full study reports were not submitted as part of this supplement. Individual patient data related to demographics, disease characteristics, prior therapy, prior transplant, treatment received, response, and response duration information was not submitted to the Agency.
- The Board and Division discussed the need for additional information from the sponsor.

Recommendations:

Board agreed that the sponsor needed to supply additional information regarding these pediatric studies.

- The Division will request that the sponsor explain the following:

- _____
  _____
  _____ If there were correspondence with the FDA regarding the ——study, please provide us with this information.
- _____
  _____
  We did not receive individual patient data related to demographics, disease characteristics, prior therapy, prior transplant, treatment received, response, and response duration.

- Once this information has been obtained, the board will decide the next steps.

Prepared by: _____ Date: _____
Debbie Avant, R.Ph.

_____ Date: _____
John Jenkins, M.D.

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/s/

Debbie Avant
4/5/05 12:18:59 PM

Pediatric Exclusivity Board

January 27, 2005

Pediatric Exclusivity Board Members Representatives	Review Division/ Office
Rosemary Roberts, OCTAP	Marty Cohen, HFD 150
Debbie Avant, Peds Team	Grant Williams, HFD-150
Edward Cox, HFD 104	Patty Garvey, HFD 150
John Jenkins	Bill Rodriquez, HFD-950
Sonal Vaid - OCC	Ramzi Dagher, HFD 150
Elizabeth Dickinson, OCC	Susan Cummins, OPT
Dena Hixon, HFD 600	
John Lazor, HFD 880	
Robert Justice, HFD 107	

Pediatric Exclusivity Determination for Gemzar (gemcitabine) Injectable – Lilly {NDA 20-509}

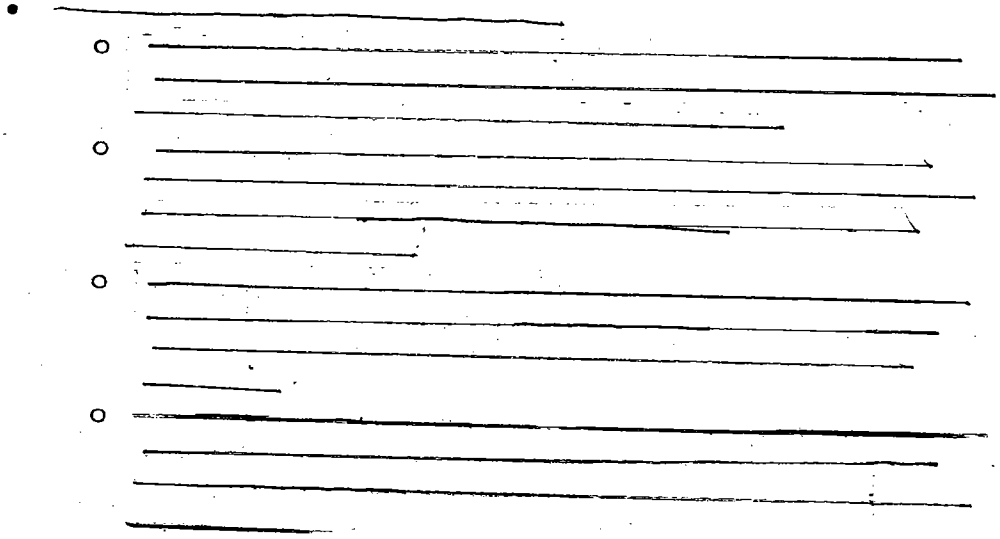
Initial Written Request:	Jan 09, 2001
Timeframe for submission of studies:	Nov 01, 2005
Date report of studies submitted:	Oct 26, 2004
Due Date for Pediatric Exclusivity Determination:	Jan 24, 2005

- During the first meeting to discuss gemcitabine on Jan 5, 2005, the division noted deviations from the Written Request:

  - Full study reports were not submitted as part of this supplement.
- The Board met to discuss Lilly's response to our request for additional information.
  - The division noted that Lilly did not realize that —— patients were required by the Written Request.
    - There was discussion that the Written Request was ambiguous since there was conflicting information in the "Types of Studies" and "Indications to be Studied" sections. In "Types of Studies" it states "Phase 2: Enrollment of at least 14 pediatric patients with each refractory ALL or AML or relapsed tumor(s)." In "Indications to be Studied" it states "Refractory or relapsed leukemia ——————
    - The division intended to obtain information on the use of gemcitabine in a broad population of pediatric oncology patients. The division stated that if the Written Request were issued today,

      ---

        - It was noted that the inclusion of several —— patients would not provide any information.
        - The division noted that based on the study findings, we got adequate information from by these studies.
    - Lilly thought that FDA accepted the standard report output from the children's cooperative groups in place of full study reports. Lilly provided the division with additional study report information, including individual patient data related to demographics, disease characteristics, prior therapy, prior transplant, treatment received, response and response duration pursuant to the board's request. While the information provided does not meet the usual standard for full study reports (no individual lab data), the division noted that any additional information provided by Lilly would not be reviewed other than for safety. Therefore, a decision was made to grant Pediatric Exclusivity.



Recommendations:

Board agreed that the sponsor needed to supply additional information regarding these pediatric studies.

- Board agreed that the sponsor fairly met all terms in the Written Request.
- Pediatric Exclusivity granted
- Division was instructed to inform the sponsor via telephone that Pediatric Exclusivity was granted. The fact that exclusivity was granted will be posted on the pediatric web site and the exclusivity will be reflected in the next monthly update to the Orange Book.

Prepared by: _____ Date: _____
Debbie Avant, R.Ph.

_____ Date: _____

John Jenkins, M.D.

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/s/

Debbie Avant
4/5/05 12:22:39 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM: IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Mail: ODS (Room 15B-08, PKLN Bldg.)		NDA 20-509	**BPCA PEDS EXCLUSIVITY**	January 27, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gemzar (gemcitabine)			April 27, 2006

NAME OF FIRM:
Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☑ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Per Section 17 of the BPCA, for one year after Peds Exclusivity is granted, FDA is to report on any adverse event related to that drug granted exclusivity.

- **Peds Exclusivity granted: January 27, 2005**
- **BPCA report due date: April 27, 2006 (15 months from date Peds Exclusivity was granted)**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Debbie Avant	☑ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Debbie Avant
1/28/05 04:13:02 PM

Garvey, Patricia

From: Garvey, Patricia
Sent: Wednesday, April 13, 2005 2:44 PM
To: 'Colleen M Mockbee'
Subject: RE: Gemzar 20-509 S033 label

hello Colleen,

The clinical team has reviewed the minor revisions and it is acceptable.

Patty
-----Original Message-----
From: Colleen M Mockbee [mailto:MOCKBEE_COLLEEN_M@LILLY.COM]
Sent: Wednesday, April 13, 2005 1:25 PM
To: GarveyP@cder.fda.gov
Subject: Gemzar 20-509 S033 label

Hi Patty,

I got your message and look forward to the action date to finalize the pediatric submission. There is just a minor change that we anticipated FDA might propose and we are agreeable to. The proposed label change Lilly submitted includes ——— As we (Lilly and FDA) previously discussed, while ——— ——— Thus, it may not be appropriate to leave the sentence as we originally proposed. I am including the proposed text we submitted with the 5 words we would agree are appropriate to remove shown in red with strikethrough.

Pediatric Patients — ——— The effectiveness of Gemzar in pediatric patients has not been demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with —— refractory leukemia ——— and determined that the maximum tolerated dose was 10 mg/m2/min for 360 minutes three times weekly followed by a one week rest period. Gemzar 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/m2/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.

Please let me know if you have any questions or if there is anything I need to do,
Colleen

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-509

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Dr. Debasish Roychowdhury
Director
U.S. Regulatory Affairs

Dear Dr. Roychowdhury:

Please refer to the Written Request, originally issued on January 9, 2001, that you received from the Center for Drug Evaluation and Research, as well as the amendment issued in July 2002, from the Office of Counter-Terrorism and Pediatric Drug Development.

BPCA § 18: Minority Children and Pediatric Exclusivity Program

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

> *Format of reports to be submitted:*
> In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request issued or re-issued under BPCA and filed by FDA, regardless of the following circumstances:

(1) the type of response to the Written Request (complete or partial);
(2) the status of the supplement (withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e. approval, approvable, not approvable); or
(4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at [http://www.fda.gov/cder/pediatric/Summaryreview.htm] and publish in the Federal Register a notification of availability.

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

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/s/

Dianne Murphy
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