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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-509

Trade Name: Gemzar

Generic Name: (gemcitiabine hydrochloride)

Sponsor: Eli Lilly and Company

Approval Date: May 15, 1996

Indications: For the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-509

CONTENTS

Reviews / Information Included in this NDA Review.

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Pharmacology Review(s)	
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-509

Food and Drug Administration
Rockville MD 20857

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

MAY 15 1996

Attn: Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

Dear Dr. Franson:

Please refer to your February 2, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar, (gemcitabine hydrochloride) for Injection.

We acknowledge receipt of your amendments dated April 17, May 9, June 1 and 19, July 26, September 28, and October 2, 1995, as well as January 9, March 1 and 13, April 3, 17 and 24, and May 1 and 10, 1996.

This new drug application provides for the first-line treatment of patients with 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.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved as effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug. Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-509. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

NDA 20-509

Page 2

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21CFR 314.80 and 314.81.

If you have any questions, please contact Linda McCollum, Consumer Safety Officer, at (301) 594-5771.

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

Appears This Way
On Original

NDA 20-509

Page 3

cc:

Original NDA 20-509

HFD150/Div. files

HFD-150/G.Schechter, R.Justice, P.Dietze, E.Tolgyesi, D.Lee-Ham, J.DeGeorge,
L.Kaus, A.Rahman, S.Wang, C.Gnecco

HFD151/CSO/L.McCollum

HFD-710/G. Chi (with labeling)

HFD-2/M.Lumpkin

HFD-101/L.Carter

HFD-101/L.Carter (with labeling)

HFD-810/C.Hoiberg

DISTRICT OFFICE

HF-2/Medwatch (with labeling)

HFD-80 (with labeling)

HFD-40/DDMAC (with labeling)

HFD-613 (with labeling)

HFD-735/(with labeling) - for all NDAs & supplements for adverse reaction changes

HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

HFD-021/J.Treacy (with labeling)

drafted: ljm/April 17, 1996/rev. 051596

r/d Initials: Pease/050196
Schechter/051596
Justice/051596
Dietze/042496
Tolgyesi/050196
Lee-Ham/042496
DeGeorge/042496
Rahman/051596
Wang/
Gnecco/051596

Final: Justice/051596

APPROVAL (AP)
doc. id. actn-ltr.ap

17 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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APPROVABLE LETTER



NDA 20-509

Food and Drug Administration
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MAY 2 1996

Attn: Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

Dear Dr. Franson:

Please refer to your February 2, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemzar (gemcitabine hydrochloride) for Injection.

We acknowledge receipt of your amendments dated April 17, May 9, June 1 and 19, July 26, September 28, and October 2, 1995, as well as January 9, March 1 and 13, April 3, 17, 23 and 24, 1996.

We have completed the review of this application as submitted on February 2, 1995 with draft labeling dated March 13, 1996, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments:

1. The Safety Review (Clinical Amendment) submitted March 13, 1996 contained information indicating that there are differences in median dose in mg/m^2 by age and gender, but no information was provided about differences in dose reductions by age and gender. Furthermore, the number of persons at risk in each category (males \leq age 65 or $>$ age 65, females \leq age 65 or $>$ age 65) for each cycle was not provided, so that an accurate assessment of the dosing information in the label could not be made. You provided further information in a facsimile on April 26, 1996 and this information is under review.

While no qualitative differences in the toxicity profile were discernable from the information submitted, you were asked to provide further information to determine if the degree of certain treatment-related symptoms and certain WHO Grade 3/4 laboratory toxicities are different for patients (men or women) less than age 65 as compared to patients over age 65. This information was also received on April 26 and is currently being reviewed.

Based on preliminary review of the information received on April 25 and 26, differences in drug tolerance in the elderly and in women are evident. Labeling will be changed to reflect this after review of this information.

2. On page 12 in the *Gastrointestinal* subsection you imply _____

3. In the *Renal* subsection on page 12 the incidence of HUS was 6/2429 patients (0.25%).

The following sentences must be added to the labeling. "Four patients developed HUS on Gemzar therapy, two immediately post therapy. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required."

4. Please insert a table in the *Adverse Reactions* section, on page 11, comparing the major toxicities of Gemzar to 5-FU based on the pivotal trial, JHAY.

In addition, it will be necessary for you to submit revised draft labeling identical to the enclosed marked-up draft labeling with the above revisions. Where there are blanks please provide the information needed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact Linda McCollum, Consumer Safety Officer, at Telephone: (301) 594-5771.

Sincerely yours,

Handwritten signature of Robert Temple and the date 5/2/96.

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Marked up draft labeling

NDA 20-509

Page 4

cc:

Original NDA 20-509

HFD-150/Div. Files

HFD-2/M.Lumpkin

HFD-80

HFD-150/Schechter, Justice, Dietze, Tolgyesi, Lee-Ham, DeGeorge, Kaus, Rahman,
Wang, Gnecco

HFD-151/L.McCollum

HFD-101/L.Carter

DISTRICT OFFICE

HFD-40/DDMAC (with draft labeling)

drafted: ljm/April 17, 1996/rev. 043096/050196/050296

r/d Initials: Pease/050196

Schechter/050196

Justice/DeLap for RJ 050196

Dietze/042496

Tolgyesi/050196

Lee-Ham/042496

DeGeorge/042496

Rahman/042596

Wang/

Gnecco/050196

*Duplicate
5-2-96*

Final: Justice/

APPROVABLE (AE)

doc. id. actn-ltr.ae

18 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

LABELING

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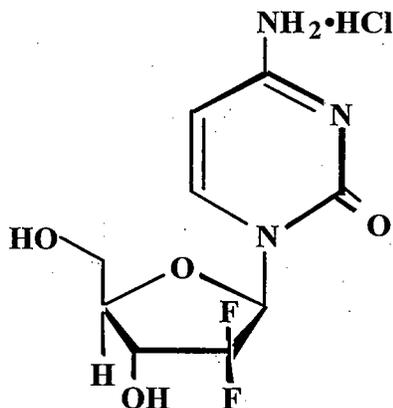
GEMZAR®
(GEMCITABINE HCl)
FOR INJECTION

5

DESCRIPTION

6 Gemzar® (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity.
7 Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).

8 The structural formula is as follows:



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

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

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

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CLINICAL PHARMACOLOGY

19 Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis
20 (S-phase) and also blocking the progression of cells through the G1/S-phase boundary.
21 Gemcitabine is metabolized intracellularly by nucleoside kinases to the active
22 diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of
23 gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate
24 nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits
25 ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the
26 deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate
27 nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP.
28 Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The
29 reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances
30 the incorporation of gemcitabine triphosphate into DNA (self-potential). After the
31 gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the
32 growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA
33 polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA
34 strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces
35 internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

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

43 **Human Pharmacokinetics** — Gemcitabine disposition was studied in 5 patients who received a
 44 single 1000 mg/m²/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of
 45 the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil
 46 metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The
 47 metabolite dFdU is also found in plasma. Gemcitabine plasma protein binding is negligible.

48 The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with
 49 various solid tumors. Pharmacokinetic parameters were derived using data from patients treated
 50 for varying durations of therapy given weekly with periodic rest weeks and using both short
 51 infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemzar dose varied
 52 from 500 to 3600 mg/m².

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

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

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

61 ^a Half-life for patients receiving a short infusion (<70 min).
 62

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

67 The volume of distribution was increased with infusion length. Volume of distribution of
 68 gemcitabine was 50 L/m² following infusions lasting <70 minutes, indicating that gemcitabine,
 69 after short infusions, is not extensively distributed into tissues. For long infusions, the volume of
 70 distribution rose to 370 L/m², reflecting slow equilibration of gemcitabine within the tissue
 71 compartment.

72 The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to
 73 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without
 74 undergoing further biotransformation. The metabolite did not accumulate with weekly dosing,
 75 but its elimination is dependent on renal excretion, and could accumulate with decreased renal
 76 function.

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

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

82 *Drug Interactions* — When Gemzar (1250 mg/m² on Days 1 and 8) and cisplatin (75 mg/m² on
83 Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was
84 128 L/hr/m² and on Day 8 was 107 L/hr/m². The clearance of cisplatin in the same study was
85 reported to be 3.94 mL/min/m² with a corresponding half-life of 134 hours (*see Drug*
86 *Interactions under PRECAUTIONS*).

87 CLINICAL STUDIES

88 *Breast Cancer* — Data from a multi-national, randomized Phase 3 study (529 patients) support
89 the use of Gemzar in combination with paclitaxel for treatment of breast cancer patients who
90 have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically
91 contraindicated. Gemzar 1250 mg/m² was administered on Days 1 and 8 of a 21-day cycle with
92 paclitaxel 175 mg/m² administered prior to Gemzar on Day 1 of each cycle. Single-agent
93 paclitaxel 175 mg/m² was administered on Day 1 of each 21-day cycle as the control arm.

94 The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to
95 documented disease progression and overall response rate compared to monotherapy with
96 paclitaxel as shown in Table 2 and Figure 1. Further, there was a strong trend toward improved
97 survival for the group given Gemzar based on an interim survival analysis.
98

Table 2: Gemzar Plus Paclitaxel Versus Paclitaxel in Breast Cancer

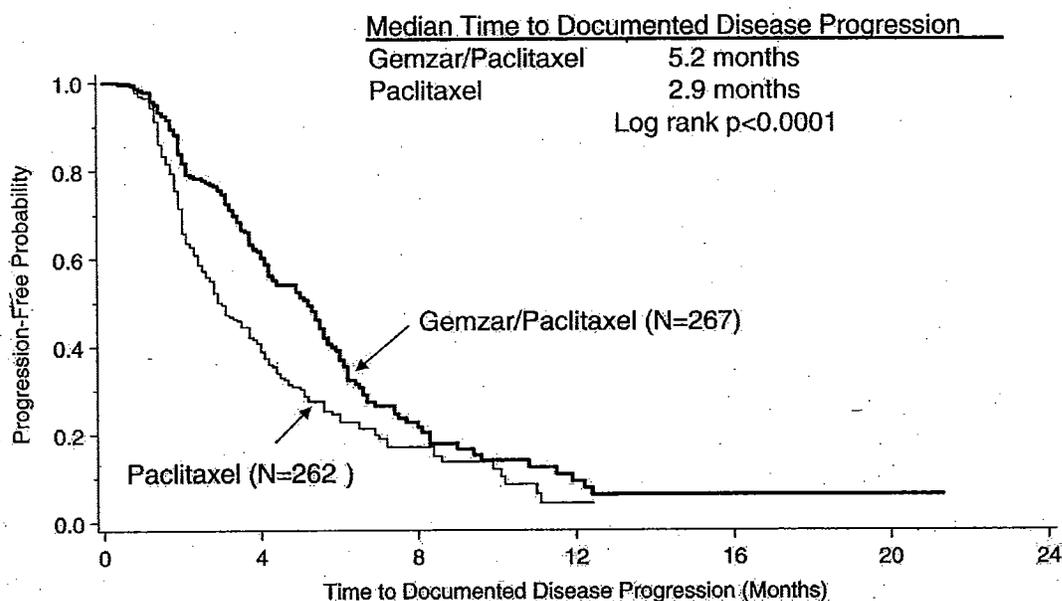
	Gemzar/Paclitaxel	Paclitaxel	
Number of patients	267	262	
Median age, years	53	52	
Range	26 to 83	26 to 75	
Metastatic disease	97.0%	96.9%	
Baseline KPS ^a ≥90	70.4%	74.4%	
Number of tumor sites			
1-2	56.6%	58.8%	
≥3	43.4%	41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	

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

99 ^a Karnofsky Performance Status.

100 ^b These represent reconciliation of investigator and Independent Review Committee assessments according to a
101 predefined algorithm.

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

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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.

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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/m² was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m² administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m² 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.

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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.

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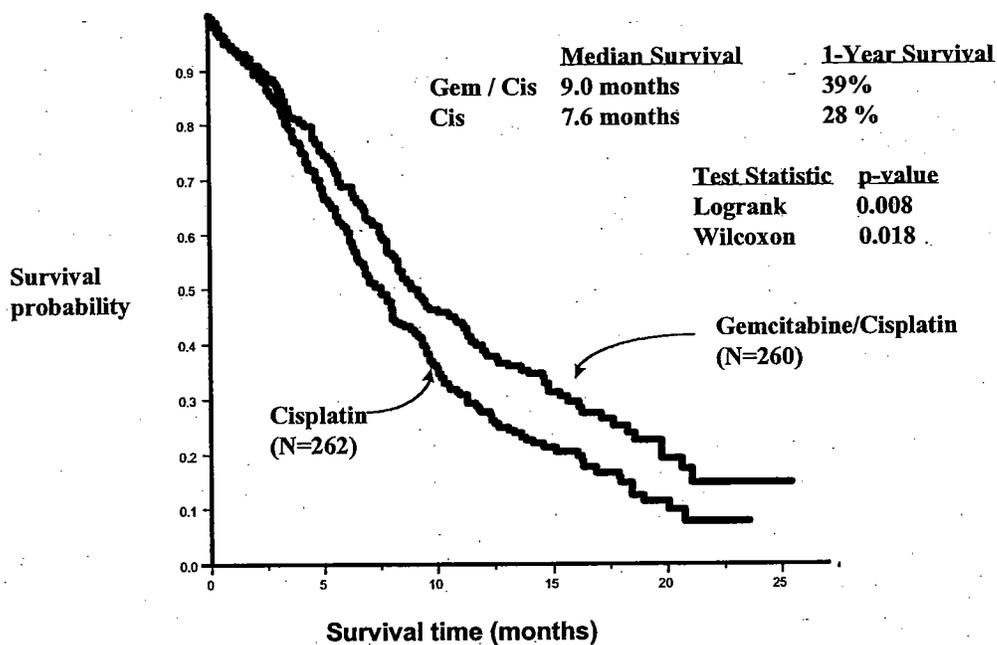
Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m² on Days 1 and 8, and cisplatin 100 mg/m² on Day 1 of a 21-day cycle or to etoposide 100 mg/m² I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m² on Day 1 on a 21-day cycle (Table 3).

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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

132 versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for
 133 the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus
 134 cisplatin arm (Logrank $p=0.015$, two-sided). The objective response rate for the Gemzar plus
 135 cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact
 136 $p=0.01$, two-sided).

137 **Quality of Life (QOL):** QOL was a secondary endpoint in both randomized studies. In the
 138 Gemzar plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which
 139 assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the
 140 study of Gemzar plus cisplatin versus etoposide plus cisplatin, QOL was measured using the
 141 EORTC QLQ-C30 and LC13, which assessed physical and psychological functioning and
 142 symptoms related to both lung cancer and its treatment. In both studies no significant differences
 143 were observed in QOL between the Gemzar plus cisplatin arm and the comparator arm.
 144



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

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

Trial	28-day Schedule ^a			21-day Schedule ^b		
	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%	

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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

^a 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m² on Days 1, 8, and 15 and cisplatin 100 mg/m² on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m² on Day 1 every 28 days.

^b 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m² on Days 1 and 8 and cisplatin 100 mg/m² on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m² on Day 1 and I.V. etoposide 100 mg/m² on Days 1, 2, and 3 every 21 days.

^c Karnofsky Performance Status.

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

N/A Not applicable.

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Pancreatic Cancer — Data from 2 clinical trials evaluated the use of Gemzar in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

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

i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status

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(Karnofsky Performance Scale) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occurring during the first 12 weeks of therapy.

OR:

- ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain ($\geq 7\%$ increase maintained for ≥ 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/m² 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.

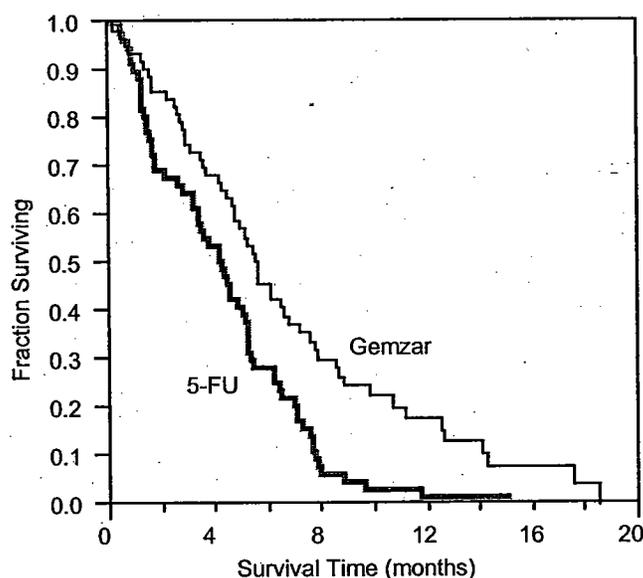
^b Kaplan-Meier estimates.

^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.

200 Clinical benefit response was achieved by 14 patients treated with Gemzar and 3 patients
 201 treated with 5-FU. One patient on the Gemzar arm showed improvement in all 3 primary
 202 parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on
 203 the Gemzar arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption
 204 and/or pain intensity with stable performance status. Two patients on the Gemzar arm showed
 205 improvement in analgesic consumption or pain intensity with improvement in performance
 206 status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic
 207 consumption with improvement in performance status. No patient on either arm achieved a
 208 clinical benefit response based on weight gain.
 209



210
 211 **Figure 3: Kaplan-Meier Survival Curve.**
 212

213 The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar
 214 in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a
 215 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median
 216 survival of 3.9 months.

217 *Other Clinical Studies* — When Gemzar was administered more frequently than once weekly
 218 or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1
 219 study of Gemzar to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed
 220 that patients developed significant hypotension and severe flu-like symptoms that were
 221 intolerable at doses above 10 mg/m². The incidence and severity of these events were
 222 dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only
 223 65 mg/m² (30-minute infusion) and 150 mg/m² (5-minute bolus). The dose-limiting toxicities
 224 were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess
 225 the maximum tolerated infusion time, clinically significant toxicity, defined as
 226 myelosuppression, was seen with weekly doses of 300 mg/m² at or above a 270-minute infusion
 227 time. The half-life of gemcitabine is influenced by the length of the infusion (*see CLINICAL*
 228 **PHARMACOLOGY**) and the toxicity appears to be increased if Gemzar is administered more
 229 frequently than once weekly or with infusions longer than 60 minutes (*see WARNINGS*).

230

INDICATIONS AND USAGE

231 Therapeutic Indications

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

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

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

241

CONTRAINDICATION

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

244

WARNINGS

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

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

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

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

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

264 *Pregnancy* — Pregnancy Category D. Gemzar can cause fetal harm when administered to a
265 pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate,
266 incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended
267 human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused
268 pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the
269 recommended human dose on a mg/m² basis). Embryotoxicity was characterized by decreased
270 fetal viability, reduced live litter sizes, and developmental delays. There are no studies of Gemzar
271 in pregnant women. If Gemzar is used during pregnancy, or if the patient becomes pregnant
272 while taking Gemzar, the patient should be apprised of the potential hazard to the fetus.

273

PRECAUTIONS

274 *General* — Patients receiving therapy with Gemzar should be monitored closely by a physician
275 experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and
276 do not need to result in discontinuation, although doses may need to be withheld or reduced.

277 There was a greater tendency in women, especially older women, not to proceed to the next
278 cycle.

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

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

285 *Carcinogenesis, Mutagenesis, Impairment of Fertility* — Long-term animal studies to evaluate
286 the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward
287 mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo*
288 mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister
289 chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled
290 DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose
291 on a mg/m² basis) in male mice had an effect on fertility with moderate to severe
292 hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility
293 was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the
294 human dose on a mg/m² basis) and fetotoxicity or embryoletality was observed at
295 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m² basis).

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

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

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

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

315 *Pediatric Patients* — Gemzar has not been studied in pediatric patients. Safety and
316 effectiveness in pediatric patients have not been established.

317 *Patients with Renal or Hepatic Impairment* — Gemzar should be used with caution in patients
318 with preexisting renal impairment or hepatic insufficiency. Gemzar has not been studied in
319 patients with significant renal or hepatic impairment.

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

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

ADVERSE REACTIONS

325
326 Gemzar has been used in a wide variety of malignancies, both as a single-agent and in
327 combination with other cytotoxic drugs.

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

331 The data in Table 5 are based on 979 patients receiving Gemzar as a single-agent administered
332 weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar
333 starting doses ranged from 800 to 1250 mg/m². Data are also shown for the subset of patients
334 with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO
335 Grade 3 or 4) adverse events were generally similar in the single-agent safety database of
336 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the
337 single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of
338 patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse
339 reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

340 All WHO-graded laboratory events are listed in Table 5, regardless of causality.
341 Non-laboratory adverse events listed in Table 5 or discussed below were those reported,
342 regardless of causality, for at least 10% of all patients, except the categories of Extravasation,
343 Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and
344 Infection categories. Table 6 presents the data from the comparative trial of Gemzar and 5-FU in
345 pancreatic cancer for the same adverse events as those in Table 5, regardless of incidence.
346

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

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

348 ^a N=699-974; all patients with laboratory or non-laboratory data.

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

350 ^c N=979.

351 ^d Regardless of causality.

352 ^e Table includes non-laboratory data with incidence for all patients $\geq 10\%$. For approximately 60% of the patients,
 353 non-laboratory events were graded only if assessed to be possibly drug-related.
 354

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

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

356 ^a N=58-63; all Gemzar patients with laboratory or non-laboratory data.

357 ^b N=61-63; all 5-FU patients with laboratory or non-laboratory data.

358 ^c Regardless of causality.

359 ^d Non-laboratory events were graded only if assessed to be possibly drug-related.

360

361 *Hematologic* — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity
 362 with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or
 363 thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence
 364 of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was

365 reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients
366 should be monitored for myelosuppression during Gemzar therapy and dosage modified or
367 suspended according to the degree of hematologic toxicity (*see* **DOSAGE AND**
368 **ADMINISTRATION**).

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

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

378 *Renal* — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical
379 findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of
380 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on
381 Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the
382 patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or
383 LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of
384 serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure
385 may not be reversible even with discontinuation of therapy and dialysis may be required (*see*
386 *Renal under Post-marketing experience*).

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

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

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

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

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

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

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

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

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

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

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

420 **Combination Use in Non-Small Cell Lung Cancer:** In the Gemzar plus cisplatin vs. cisplatin
421 study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin injections
422 on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were required in
423 greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations
424 for possibly drug-related adverse events occurred in 15% of patients on the combination arm and
425 8% of patients on the cisplatin arm. With a median of 4 cycles of Gemzar plus cisplatin
426 treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly
427 treatment-related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of
428 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse
429 events.

430 In the Gemzar plus cisplatin vs. etoposide plus cisplatin study, dose adjustments occurred with
431 20% of Gemzar injections and 16% of cisplatin injections in the Gemzar plus cisplatin arm
432 compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus
433 cisplatin arm. With a median of 5 cycles of Gemzar plus cisplatin treatment, 15 of 69
434 patients (22%) experienced 15 hospitalizations due to possibly treatment-related adverse events.
435 With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%)
436 experienced 22 hospitalizations due to possibly treatment-related adverse events. In patients who
437 completed more than one cycle, dose adjustments were reported in 81% of the Gemzar plus
438 cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study
439 discontinuations for possibly drug-related adverse events occurred in 14% of patients on the
440 Gemzar plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The
441 incidence of myelosuppression was increased in frequency with Gemzar plus cisplatin
442 treatment (~90%) compared to that with the Gemzar monotherapy (~60%). With combination
443 therapy Gemzar dosage adjustments for hematologic toxicity were required more often while
444 cisplatin dose adjustments were less frequently required.

445 Table 7 presents the safety data from the Gemzar plus cisplatin vs. cisplatin study in non-small
446 cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug
447 combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths,
448 including 3 resulting from myelosuppression with infection and 1 case of renal failure associated
449 with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm.
450 Nine cases of febrile neutropenia were reported on the combination therapy arm compared to
451 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the Gemzar plus
452 cisplatin arm.

453 Myelosuppression occurred more frequently on the combination arm, and in 4 possibly
454 treatment-related deaths myelosuppression was observed. Sepsis was reported in 4% of patients
455 on the Gemzar plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were
456 required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm.
457 Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin
458 arm. However, severe hemorrhagic events were rare. Red blood cell transfusions were required in
459 39% of the patients on the Gemzar plus cisplatin arm, versus 13% on the cisplatin arm. The data
460 suggest cumulative anemia with continued Gemzar plus cisplatin use.

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

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

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

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

491

**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

492 Grade based on Common Toxicity Criteria (CTC). Table includes data for adverse events with incidence $\geq 10\%$ in
493 either arm.

494 ^a N=217-253; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1000 mg/m² on
495 Days 1, 8, and 15 and cisplatin at 100 mg/m² on Day 1 every 28 days.

496 ^b N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 every
497 28 days.

498 ^c Regardless of causality.

499 ^d Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

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

501

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/m² on Days 1 and 8 and cisplatin at 100 mg/m² 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/m² on Day 1 and I.V. etoposide at 100 mg/m² 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.

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512 **Combination Use in Breast Cancer:** In the Gemzar plus paclitaxel versus paclitaxel study,
 513 dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the
 514 combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar
 515 doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel
 516 doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemzar plus paclitaxel arm and
 517 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were
 518 two deaths on study or within 30 days after study drug discontinuation that were possibly
 519 drug-related, one on each arm.

520 Table 9 presents the safety data occurrences of $\geq 10\%$ (all grades) from the Gemzar plus
 521 paclitaxel versus paclitaxel study in breast cancer.

522

**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

523 ^a Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades $\geq 10\%$).

524 ^b Regardless of causality.

525 ^c Non-laboratory events were graded only if assessed to be possibly drug-related.

526

527 The following are the clinically relevant adverse events that occurred in $>1\%$ and $<10\%$ (all
528 grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse
529 events (Gemzar plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%),
530 infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity
531 (0 versus 0.8%).

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

534 **Post-marketing experience:** The following adverse events have been identified during
535 post-approval use of Gemzar. These events have occurred after Gemzar single-agent use and
536 Gemzar in combination with other cytotoxic agents. Decisions to include these events are based
537 on the seriousness of the event, frequency of reporting, or potential causal connection to Gemzar.

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

541 *Vascular Disorders* — Vascular toxicity reported with Gemzar includes clinical signs of
542 vasculitis, which has been reported very rarely. Gangrene has also been reported very rarely.

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

545 *Hepatic* — Serious hepatotoxicity including liver failure and death has been reported very
546 rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic
547 drugs.

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

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

558

OVERDOSAGE

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

564

DOSAGE AND ADMINISTRATION

565 *Gemzar is for intravenous use only.*

Adults

Single-Agent Use:

568 *Pancreatic Cancer* — Gemzar should be administered by intravenous infusion at a dose of
569 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates

570 reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should
571 consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

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

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

579

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

580

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

585 Patients treated with Gemzar who complete an entire cycle of therapy may have the dose for
586 subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and
587 platelet nadirs exceed 1500 x 10⁶/L and 100,000 x 10⁶/L, respectively, and if non-hematologic
588 toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of
589 Gemzar at the increased dose, the dose for the next cycle can be further increased by 20%,
590 provided again that the AGC and platelet nadirs exceed 1500 x 10⁶/L and 100,000 x 10⁶/L,
591 respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

592 Combination Use:

593 *Non-Small Cell Lung Cancer* — Two schedules have been investigated and the optimum
594 schedule has not been determined (*see CLINICAL STUDIES*). With the 4-week schedule,
595 Gemzar should be administered intravenously at 1000 mg/m² over 30 minutes on Days 1, 8, and
596 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m² on Day 1
597 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered
598 intravenously at 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at
599 a dose of 100 mg/m² should be administered intravenously after the infusion of Gemzar on
600 Day 1. See prescribing information for cisplatin administration and hydration guidelines.

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

608 In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and
609 nausea/vomiting, therapy with Gemzar plus cisplatin should be held or decreased by 50%
610 depending on the judgment of the treating physician. During combination therapy with cisplatin,
611 serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully

612 monitored (Grade 3/4 serum creatinine toxicity for Gemzar plus cisplatin was 5% versus 2% for
613 cisplatin alone).

614 *Breast Cancer* — Gemzar should be administered intravenously at a dose of 1250 mg/m² over
615 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at
616 175 mg/m² on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients
617 should be monitored prior to each dose with a complete blood count, including differential
618 counts. Patients should have an absolute granulocyte count $\geq 1500 \times 10^6/L$ and a platelet count
619 $\geq 100,000 \times 10^6/L$ prior to each cycle.

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

623

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

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

624

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

629 Gemzar may be administered on an outpatient basis.

630 *Instructions for Use/Handling* — The recommended diluent for reconstitution of Gemzar is
631 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the
632 maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at
633 concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be
634 avoided.

635 To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of
636 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a
637 gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume
638 of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total
639 volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of
640 the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate
641 amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride
642 Injection to concentrations as low as 0.1 mg/mL.

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

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

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

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

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

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

664 HOW SUPPLIED

665 Vials:

666 200 mg white, lyophilized powder in a 10-mL size sterile single use vial (No. 7501)

667 NDC 0002-7501-01

668 1 g white, lyophilized powder in a 50-mL size sterile single use vial (No. 7502)

669 NDC 0002-7502-01
670

671 Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined
672 controlled room temperature as "A temperature maintained thermostatically that encompasses the
673 usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean
674 kinetic temperature calculated to be not more than 25°C; and that allows for excursions between
675 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses."

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-509

MEDICAL REVIEW

FEB 14 1996

GEMCITABINE (GEMZAR^R)
NDA-20509

DECEMBER 11, 1995
REVISED: FEBRUARY 12, 1996

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I. INTRODUCTION:

NDA 20509 requests the approval of Gemzar^R (gemcitabine hydrochloride) for use in the palliative treatment of advanced or metastatic pancreatic cancer in previously untreated patients or patients refractory to fluorouracil therapy. Case reports forms were submitted for review from four clinical trials: (1) one phase III trial (JHAY) in which gemcitabine is compared to 5-FU in previously untreated patients in a single blinded, randomized, controlled study in which the primary end-point is clinical benefit response, (2) one phase II trial (JHAZ) in which gemcitabine is used in patients with advanced or metastatic pancreatic cancer refractory to 5-FU in which the primary endpoint was clinical benefit response, and (3) two phase II trials (JHAL ext., EO12) in previously untreated patients with advanced or metastatic pancreatic cancer. A study report (JHAL) for a fifth trial using Gemcitabine at a lower dose in pancreatic cancer was included in the NDA and is reviewed also.

The original IND was submitted in January, 1987. At the End-of-Phase II meeting and in a conference call held in early 1992, the sponsor proposed an innovative primary endpoint for the two pivotal trials (JHAY, JHAZ) clinical benefit response. Clinical benefit response is a composite endpoint. The three equally weighted components include: (1) the pain "index" which includes pain intensity scoring and analgesia consumption; (2) performance status, and (3) weight change. Traditional endpoints such as time to progression, time to treatment failure, and survival were proposed as secondary endpoints. In the phase II trials the "traditional" primary endpoints of response rate, time to progression, and survival were used with measurement of analgesia consumption, performance status, and weight as part of the data collection.

Clinical Benefit Response, as defined in the pivotal and supporting trials, is based on statistical modeling of the information collected in the phase II trials regarding change in performance status, analgesia consumption, and weight. These parameters were noted to be relatively stable for those patients enrolled on JHAL, JHAL (ext), and EO12. While the objective tumor response parameter measurements were not much different from the literature reports for other chemotherapeutic agents, the stabilization of these "quality of life" parameters was impressive. The idea of measurement of a clinical benefit response as a primary efficacy endpoint with "traditional" parameters as secondary endpoints then evolved. Clinical benefit response type of parameters have not been measured and modelled in pancreatic cancer patients receiving other chemotherapeutic agents, radiation, or best supportive care.

This review will focus on the pivotal trials (JHAY) and the supporting phase II trial (JHAY). Two phase II trials will be presented briefly to provide further background information about objective efficacy parameters and safety issues. A review of the JHAL study report is also included primarily for review of safety aspect.

All case reports submitted were reviewed and the data with regard to objective measures (response, time to progression, time to treatment failure, and survival) in this review are based on the medical reviewer's database. With regard to clinical benefit parameters, a more extensive review will be presented by Biometrics. The patient database used for statistical calculations, response information,

description of the clinical course of the clinical benefit responders, and a summary of patients removed from study due to adverse reactions is included in the appendix following each study.

II. DRUG DESCRIPTION:

A. General Information:

Trade Name: Gemzar^R

Generic Name: gemcitabine hydrochloride

Chemical Name: 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β isomer)

Chemical Formula: $C_9H_{11}F_2N_3O_4 \cdot HCL$

Mechanism of Action: Inhibits DNA synthesis, blocks progression of cell through the G₁/S-phase boundary

Metabolism: Nucleoside kinases phosphorylate the drug to an active diphosphate (dFdCDP) and triphosphate (dFdCTP) which when intercalated into DNA result in inhibition of further DNA synthesis. With incorporation of the gemcitabine nucleotide (dFdCTP) into the DNA strand after addition of one further nucleotide, DNA polymerase epsilon is unable to remove the defective nucleotide (dFdCTP) and repair the strand which results in cellular apoptosis

B: Human Pharmacokinetics:

The infused drug is metabolized by nucleoside kinases to an active diphosphate (dFdCDP) and triphosphate (dFdCTP). The drug is further metabolized to dFdU (2'-deoxy-2',2'-difluorouridine). Urinary excretion of 92-98% of the drug occurs within one week. The urinary metabolites include unchanged gemcitabine (10%), and dFdU (~ 90%).

Gemcitabine exhibits linear pharmacokinetics following a two compartment model with a half-life of 11-26 minutes when a short infusion schedule (<70 minutes) is used. With longer infusion times the half-life varies from 18.5-57.1 minutes due to increased tissue distribution not seen with the shorter infusions. Renal clearance of the drug accounts for only 10% of the systemic clearance. Metabolite clearance (dFdU) is dependent on renal clearance and tissue accumulation of metabolite occurs with decreased renal function. The mean apparent clearance of dFdU is 2.5 L/hr/m².

The effects of decreased renal or hepatic function on drug have not been assessed. Clearance is affected by gender and age. Clearance in women is 75% of the clearance in men. Clearance decreases with age with the clearance of a 70 year old is approximately half of the clearance in a 29 yr old regardless of

sex. At a dose of 1000 mg/m² given weekly the decreased clearance in women and the elderly should not necessitate a change in the dosing regimen according to the sponsor.

III. CHEMISTRY

See Chemistry Review. Some unresolved chemistry issues are pending regarding synthesis methodology.

IV. PHARMACOLOGY:

See Pharmacology Review

V. BACKGROUND INFORMATION -PANCREATIC CANCER

Between 25,000 and 30,000 thousand new cases of pancreatic cancer will be diagnosed in the 1995 and over 90% of those diagnosed with this disease will die within one year. Only those patients with tumors located within the pancreas without proximity to major organs or vital structures will have a chance for surgical cure. Various chemotherapeutic agents have been used for treatment of this disease with little success.

Fluorouracil was approved for use in pancreatic cancer after the Food and Drug Administration evaluated reports from the National Academy of Science-National Research Council Drug Efficacy Study Group. In the Federal Register, Volume 35, No. 205, Wednesday October 21, 1970 Fluorouracil was recommended for the "palliative management of carcinoma of the breast, colon or rectum, stomach, and pancreas in carefully selected patients who are considered incurable by surgery or other means."

In a paper by Cullinan et al¹ results of a multicenter study of three regimens [fluorouracil (FU); fluorouracil (FU) and doxorubicin (DOX); and, fluorouracil, doxorubicin, and mitomycin (FAM)] used in the treatment of pancreatic and gastric cancer were analyzed for response, time to progression, survival, and toxicities, as well as palliation parameters. For the 211 pancreatic patients randomized to three arms, no meaningful data with regard to response could be reported due to the small number of patients with measurable disease. The median interval to progression was nine weeks. No significant difference between arms was detected with regard to TTP. The median survival for all pancreatic patients was 22 week (no significant difference between treatment arms).

Parameters of palliation were evaluated. Fifteen per cent of the patients showed a weight gain on study, 20% had an improvement in performance status, and 26% claimed symptomatic improvement. The authors point out that the some or all of the improvement in palliation might be attributed to improved supportive care. Toxicities on the FU only arm (gastric and pancreatic patients) included:

¹ S.A.Cullinan et al. "A Comparison of Three Chemotherapeutic Regimens in the Treatment of Advanced Pancreatic and Gastric Carcinoma". JAMA 253 (14):2061-2067, 1985.

(1) leukopenia < 2000/ul - 29%, (2) thrombocytopenia < 130,000/ul - 36%, < 50,000/ul - 1, (3) anorexia - 13%, (4) nausea - 64%, (5) vomiting - 41%, (6) diarrhea - 44%, (7) stomatitis - 46%, and alopecia - 20%. The authors question whether any of the chemotherapeutic regimens in this study are "capable of producing any real palliation over and above what could be achieved by simple symptomatic and supportive measures alone."

VI. PIVOTAL TRIAL REVIEW

Title: JHAY: Gemcitabine vs. 5-FU in a Randomized Trial as First Line Palliative Therapy in Patients with Carcinoma of the Pancreas

In the introduction to B9E-MC-JHAY the following statement is made: "Within the past five years, the Food and Drug Administration has suggested in various forums that efficacy endpoints other than survival improvement can serve as the basis of approval of an oncolytic agent. Such alternative endpoints have a common denominator of measurable clinical benefit that favorably affects the quality of life and reduces patient suffering without necessarily effecting a survival improvement. Coincident with this shift toward exploring alternative endpoints as valid efficacy measures has been the recent rapid evolution and maturation of reliable instruments to reproducibly quantitate improvement in the overall status and quality of life of the patient." The clinical benefit endpoints measured in this study are "published and recognized as valid, reproducible, and reliable and define as clinical benefit responders only those patients who have a measurable improvement in symptoms in the absence of concomitant deterioration." This trial proposes to compare the clinical benefit response of gemcitabine as compared to 5-FU in a randomly controlled trial in which patients and performance status evaluators are blinded with regard to therapy.

Protocol Summary:

Objectives:

Primary: To establish an advantage in clinical benefit of gemcitabine over 5-FU in patients with cancer of the pancreas as measured by significant improvement in pain, performance status, or weight change.

Secondary:

- (1) To compare the treatment arms with respect to time to progressive disease (TTP), survival, duration of clinical benefit response, and univariate assessments of the primary variables, and
- (2) To assess differences in the population pharmacokinetics in patients treated with gemcitabine and 5-FU.

Design:

Multicenter, single blind (efforts will be made to blind performance status evaluators and patients with

regard to treatment), two armed, randomized, controlled study with a lead-in period of two to seven days to stabilize and characterize the patient's analgesic consumption and pain intensity followed by randomization at a centralized location with stratification based on four factors: pain intensity (baseline score ≥ 30 or < 30), analgesic consumption (baseline score ≥ 60 mg morphine equivalents or < 60 mg morphine equivalents), performance status (baseline KPS ≥ 70 or < 70), and investigator site (one per stratum). Randomization was scheduled at time of pain stabilization just prior to initiation of the study drug. Randomization was dynamically allocated.

The stratification criteria were amended on February 25, 1994 to the following: pain intensity (baseline score ≥ 20 or < 20), analgesia consumption (baseline score ≥ 10 or < 10), performance status (baseline KPS ≥ 80 or ≤ 70). Justification for this amendment was as follows: Change in the cut-off values would allow for baseline values which would provide a better 50/50 split between high and low strata for each prognostic factor.

Sample Size:

A sample size of one hundred twenty patients (60/arm) would allow for an 80% chance of detecting a difference between an arm having a true clinical benefit response of 0.30 and an arm having a true clinical benefit of 0.10 with a 5% chance of concluding falsely that there is a difference between arms. An amendment to increase the sample size was submitted on December 14, 1993 to allow the sample size of to 136 patients in order to insure that the required 120 patients are qualified for efficacy analysis.

Dosing Schedule:

Gemcitabine:

Gemcitabine was administered intravenously starting at 1000 mg/m^2 over thirty minutes once weekly for up to seven weeks for the first cycle, (**By definition on the gemcitabine arm the length of the first cycle could vary from three to eight weeks depending on the degree of toxicity encountered following each dose.**), then weekly three out of four weeks until progression or until a decision was made that discontinuation of therapy was in the patient's best interest. For patients who achieved a complete response up to eight additional cycles could be given. For patients with \leq Grade I toxicity during one cycle dose may be escalated by 25% for the next cycle. A second dose escalation of 20% of the dose in the previous cycle is permitted for those patients who have \leq Grade I toxicity in the previous cycle.

For hematological toxicity in the original protocol, gemcitabine dose reduction was:

- (1) 25% for AGN 500-999/ul or platelets 50-99,000/ul;
- (2) hold for AGN < 500 /ul or platelets $< 49,900$ /ul and resume next cycle with a 25% dose reduction.

The dose reduction schedule was amended on July 2, 1992 as follows:

- (1) 25% for AGN 1250-1500/ul or platelets 50,000-99,999/ul;
- (2) 50% for AGN 1000-1249/ul or platelets 50,000-74,900/ul;

(3) hold for AGN < 1000/ul or platelets < 50,000/ul, resume with 25% dose reduction next cycle.

For non-hematological toxicities the original dose modification schedule was:

- (1) WHO Grade 0-2: 100% of dose;
- (2) WHO Grade 3: 100% if nausea, vomiting or alopecia, 50% or hold for other toxicities;
- (2) WHO Grade 4: hold.

On July 2, 1992 the dose modification schedule was amended to:

- (1) WHO 2 mucositis or diarrhea - hold for one week, if toxicity resolves, resume therapy at pretotoxicity dose;
- (2) WHO Grade III/IV mucositis or diarrhea - hold for one week and resume at 50% of the pretotoxicity dose; if no further toxicity occurs after three weeks at this level, escalate by 250 mg/m² per week to 100% of the pretotoxicity level;
- (3) WHO Grade 3 nausea, vomiting, or alopecia - 100% of dose, hold for Grade IV;
- (4) other toxicity, WHO Grade III - 50 % or hold
- (5) other toxicity, WHO Grade IV - hold dose and decrease dose 50% for next cycle.

If a patient cannot be treated for a period of six weeks due to persistent toxicity, the patient must be discontinued from study.

5-FU:

Fluorouracil was given intravenously at 600 mg/m² over thirty minutes weekly. A cycle was defined as four weeks. Dose escalation of 25% was allowed for patients who experienced ≤ Grade I WHO toxicity. A second dose escalation of 20% of the previous dose was allowed for those patient who experience ≤ Grade I toxicity with the first dose escalation.

In the original protocol, for hematological toxicities the following dose reduction schedule applied:

- (1) for AGN 1500-1999/ul or platelets 75,000-119,900/ul, 25% dose reduction;
- (2) for AGN 1000-1499/ul or platelets 50-74,900/ul, 66% dose reduction;
- (3) for AGN < 1000/ul or platelets < 50,000/ul, hold drug, resume with a 25% dose reduction for next cycle

In the amendment dated July 2, 1992 dose modifications for hematological toxicities associated with FU were changed to:

- (1) for AGN 1250-1500/ul or platelets 75,000-99,900/ul, 25% dose reduction;
- (2) for AGN 1000-1249/ul or platelets 50,000-74,500/ul, 50% dose reduction;
- (3) for AGN < 1000/ul or platelets < 50,000/ul, hold drug, resume next cycle with a 25% dose reduction.

In the original protocol for nonhematological toxicities, the dose modification schedule was as follows:

- (1) WHO Grade 0-2 - 100% of dose;
- (2) WHO Grade 3 nausea, vomiting, or alopecia - 100% of dose;
- (3) WHO Grade 3 other toxicities, 50% or hold depending on investigator discretion;
- (4) WHO grade 4, hold until toxicity resolves.

The dose modification schedule was amended as follows:

- (1) WHO Grade 0-2 100% of dose
- (2) WHO Grade 2 diarrhea or mucositis, hold; if the toxicity resolves in one week, resume at 100% dose level
- (3) WHO Grade 3 diarrhea or mucositis, hold for one week and resume at 50% of the previous dose and, if no toxicity occurs within three weeks at the lower dose, escalate dose by 100 mg/m² until patient achieves 100% of the pretotoxicity dose
- (4) WHO Grade 4, hold dose and resume at 50% when toxicity has cleared, if toxicity recurs remove patient from study

Use of marrow stimulatory factors was discouraged.

Study Population:

Inclusion Criteria:

Histologic or cytologic diagnosis of pancreatic cancer not amenable to surgical treatment

May have prior radiation as long as other sites of measurable or evaluable disease exist

Baseline Karnofsky Performance Status ≥ 50

Measurable or evaluable disease

(Measurable lesions must be bidimensional with a minimum dimensions of 1.0 x 1.0 cm defined by CT, MRI, chest x-ray, or ultrasound. Two x 2 cm. lesions on physical exam may be used as indicator lesions. Evaluable disease has only one measurable dimension. Unmeasurable disease includes lesions in previously irradiated fields, ascites, pleural effusions, blastic or mixed bony lesions, or palpable abdominal masses.)

Estimated life expectancy of 12 weeks

Patient compliance, geographic proximity to allow follow-up

Adequate bone marrow reserve:

WBC $\leq 3500/\text{ul}$,

Platelets $\geq 100,000/\text{ul}$,

Hemoglobin $\geq 9.5 \text{ gm}\%$

Age ≥ 18 years

Informed consent

If female, no childbearing potential or use of effective contraception

Exclusion Criteria:

Diagnosis of islet cell tumor of the pancreas, lymphoma of the pancreas or other malignancy except resected basal cell carcinomas, curatively resected Stage I or less carcinoma of the cervix, or other malignancy from which the patient has been disease free for five years or more

Prior CNS metastases

Baseline KPS ≥ 80 , baseline analgesic consumption ≤ 10 morphine equivalents/day, AND pain intensity score ≤ 20

Failure of pain stabilization during lead-in period
Prior chemotherapy including radiosensitizers
Nonmeasurable disease
Active infection; severe cardiac disease requiring therapy for angina, arrhythmias, or uncompensated cardiac failure; myocardial infarction within six months; severe pulmonary disease; significant neurological or psychiatric disorders
Clinically significant third space fluid collection such as ascites, pleural effusion
Concomitant radiotherapy, chemotherapy, hormonal therapy (excluding estrogen replacement during menopause or oral contraceptives, immunotherapy, or steroid therapy except topical or adrenal replacement therapy)
Radiation, steroidal therapy, or neuromuscular blocks within past three weeks
Inadequate liver function: Bilirubin > 2.0 mg/dl, SGOT (AST) or SGPT (ALT) > 3 x normal, abnormal PT or aPTT > 1.5 x normal
Inadequate renal function: creatinine > 1.5 mg/dl
Serum calcium > 11.0 mg/dl
Pregnancy, inadequate contraception, breast feeding

Efficacy Evaluations for Study Participants:

Clinical Benefit Response Measurements:

Daily analgesic consumption
Daily pain intensity information (MPAC cards)
Weekly performance status
Weekly weight

Objective Tumor Response Parameters:

Weekly vital signs, history and physical examination
Measurement of palpable masses
Weekly hand grip strength
CBC with diff, PT, aPTT at local lab
U/A, SMA-17 weekly at central lab
Chest xray pretreatment, every four weeks
EKG pretreatment, every eight weeks
CT, MRI, or ultrasound pretreatment, every four weeks

Safety Data:

Toxicity grading using WHO scale
Blood products transfusion history
Use of TPN
Resource utilization survey

Reasons for Study Discontinuation:

- Definite evidence of progression
- Physician decision discontinuation in patient's best interest
- Patient request
- Unacceptable drug toxicity
- Unresolved drug related toxicity > six weeks
- Sponsor discretion
- Completion of eight months therapy following an objective complete response

Efficacy Analysis:

Clinical Benefit Response (CBR):

Clinical Benefit Response (CBR) is a dichotomous variable based on the following primary measures: Pain Intensity, Analgesia Consumption, and Performance Status (Karnofsky Performance Status) and one secondary measure: Weight.

Definition of Primary Measures:

Pain Intensity:

Pain Intensity is evaluated using the Memorial Pain Assessment Cards (MPAC). With these cards evaluation of patient's pain is done using the following scoring system:

- (1) Pain intensity is rated daily by the patient on a linear scale from 0 (best- no pain intensity) to 100 (most severe).
- (2) Pain relief is rated daily by the patient using a linear scale where 0 = no pain relief to 100 = complete pain relief
- (3) Mood is evaluated daily using a linear scale where 0 = worst possible mood and 100 = best possible mood
- (4) A Pain Scale is used with the following grades: 1 = no pain; 2 = just noticeable pain; 3 = weak pain; 4 = mild pain; 5 = moderate pain; 6 = strong pain; 7 = severe pain; 8 = excruciating pain.

Grading of the MPAC system is as follows:

- (1) Pain intensity: Positive response is defined as a 50% decrease over baseline with the baseline ≥ 20 (positive response not attainable with baseline < 20); negative response is defined as higher than baseline and > 20); stable response means no change to a 50% decrease from baseline.
- (2) Pain Relief: Positive response is defined as a 50% improvement from baseline with the baseline ≤ 80 (positive response is not attainable with baseline > 80); negative response is defined as a pain relief score less than baseline and < 80; stable response means no change

from baseline or pain relief < 50% improved from baseline.

(3) Mood Evaluation: Positive response is defined as a 50% increase over baseline with a baseline < 80 (positive response is not attainable with baseline > 80); negative response is defined as a mood score < baseline or lower than 80; stable response is no change to < 50 % improved from baseline.

(4) Pain Scale: Positive response is 2.0 points < than baseline; negative response is 2.0 points > than baseline; stable response is no change or \pm 2.0 points from baseline

ONLY the first category pain intensity was used in this protocol in determining the PAIN INTENSITY score for Clinical Benefit Response. Other data from the MPAC was not used in the evaluation of pain intensity. If increased pain intensity was due to another cause (ie. trauma), pain intensity was considered as stable. If data was missing for more than 3 days per week, the weekly mean was considered to be missing. In each category to be considered positive a patient must have positive scores for four or more consecutive weeks for the first twelve weeks. After week twelve no negative responses could occur since a "patient's pain was expected to deteriorate due to their disease and should not be penalized by this system."

Analgesia Consumption:

All analgesics were converted to PO morphine equivalents using the following equivalence table:

Equianalgesic Dose Table

Drug	SQ or IM or IV (mg)	PO morphine equivalents (mg)
Morphine	10.0	30
Hydromorphone	1.5	8
Levophanol	2.0	4
Methadone	10	20
Oxycodone	--	20
Meperidine	75	300
Fentanyl Patch (TTS-100)		160/day
Oxymorphone 15 mg. supp.		15
Acetaminophen	650	9

The mean analgesic consumption per week was used in calculation of the analgesic response. For patients with a baseline analgesic consumption of greater than 10 mg. morphine equivalents, a positive response is attainable if there is a 50% decrease in AC for a four consecutive week period. **During the first twelve weeks of the trial, if the AC is increased over baseline and greater than 10 mg morphine equivalents, the patient has a negative AC score. After 12 weeks negative scores are regarded as stable as the patient is expected to deteriorate. Patients with no change in AC or <**

50% decrease are considered as stable.

Performance Status:

The Karnofsky Performance scale was used to evaluate performance status. Two evaluators at each center blinded to the treatment were to independently assess the score and the lower score was reported. A twenty point or more improvement in KPS with a baseline score less than 80 for a period of four consecutive weeks defines a positive responder. A twenty point or more decrease in KPS for four consecutive weeks during the first twelve weeks of the study defined a negative response during the study. Stable KPS or a change of less than twenty points for any consecutive four weeks during the first twelve weeks of trial is considered a stable responder. If a patient is removed from study because of decline in KPS the patient's response is negative. **After 12 weeks KPS, even if negative, was regarded as stable due to deterioration from disease processes.**

Scheme for Assessment of Clinical Benefit Response:

PI and AC were the initial parameters considered in the assessment of clinical benefit response. If the PI and/or AC consumption decreased > 50% from baseline for four consecutive weeks, or if PI and AC remained stable (no change from baseline) for four consecutive weeks, the patient was a potential clinical benefit responder. Performance status was then evaluated. If AC or PI had decreased, and performance status was stable or had improved from baseline, the patient was considered to have a clinical benefit response (CBR). If PI and AC were stable (less than a 50% decrease from baseline) and PS was improved ≥ 20 points from baseline for four consecutive weeks, the patient was deemed a clinical benefit responder. If PI, AC, and KPS were stable, then weight had to increase by 7% (without evidence of third space accumulation) and be maintained for four consecutive weeks for clinical benefit response to be attained.

CBR, Statistical Considerations:

Clinical benefit response rate is defined as:

$$\frac{\text{No. CBRers}}{\text{No. of Pts. Randomized to Study Drug}}$$

And if P_G = true clinical benefit response Gemcitabine arm
and if P_F = true clinical benefit response FU arm

The null and alternative hypotheses are:

$$H_0: P_G = P_F$$
$$H_A: P_G < \text{or} > P_F$$

The size of the exact binomial two-sided test with 60 patients in each arm is 0.05. This test contains 80% power to detect the following difference:

$$P_G = 0.30 \quad P_F = 0.10$$

In addition, an observed CBR rate of $18/60 = 0.30$ on gemcitabine and $6/60 = 0.10$ on FU will result in a two-sided 95% confidence interval for $P_G - P_F$ of (0.06, 0.34)

Definitions of Objective Tumor Response Parameters:

Objective Tumor Response Rates:

$$\frac{\text{No of CRs + PRs}}{\text{No. of Randomized Pts. with Measurable Disease}}$$

Complete response is the disappearance of all measurable disease for a minimum of four weeks documented by appropriate diagnostic tests and freedom from tumor related symptoms.

Partial response is a 50% decrease in the products of all diameters of all measurable disease for a minimum of four weeks documented by the appropriate diagnostic tests with no increase in other disease or the appearance of new lesions.

Stable disease is a decrease in tumor mass less than 50% or an increase in tumor mass less than 25% in the absence of new lesions. In the absence of CR or PR patients who are stable at the end of eight weeks will be considered as stable disease.

Progressive disease is the 25% increase in the sum of all products of all measurable disease, the appearance of new lesions, or a deterioration in clinical status consistent with disease progression such as the placement of biliary stents, neuromuscular block etc. (In this review development of ascites was considered as disease progression as were new findings on physical exam consistent with progression.)

Survival is determined from the time of randomization until the time of death.

Time to progressive disease is determined from the date of randomization until the time the patient is classified as having progressive disease or until the time that the patient is discontinued from study. (In this review time to progression, TTP, will be defined as the time from randomization until the time of objective progression if this occurs while on study.)

(Time to treatment failure was not defined in the protocol. Time to treatment failure is defined by the reviewer as the time from randomization to the time that the patient is off-study due to objective tumor progression, clinical progression (investigator perception of progression), adverse events, patient refusal, or death.)

Duration of Clinical Benefit Response:

To be a clinical benefit responder at least one component (PI, AC, KPS, or Wt.) must be positive with all other clinical benefit response categories positive or stable. The duration of the clinical benefit response is defined as the largest number of consecutive weeks in which the primary component (PI, AC, or KPS) on which CBR is based has no weekly back-to-back nonpositive scores (called primary positive weeks). If only one component (PI, AC, KPS, or WT) is positive, the duration of clinical benefit response is defined as the largest number of weeks in which the primary component has no weekly back to back nonpositive scores (without consideration of changes in the secondary components). **If more than one component is positive, the largest number of weeks that AT LEAST one component remains positive (no back-to-back nonpositive scores) is defined as the duration of clinical benefit response (without regard to changes in the other components).** Scores in the non-primary component(s), even if worst than baseline, did not negate clinical benefit, only the component(s) on which clinical benefit response is based must remain positive.

Study Results:

Demographics:

Table I presents the pertinent demographic data for this study. With regard to stage of disease the CRF did not provide adequate documentation of stage. The date of diagnosis, the histological stage, and the clinical stage were entered, but no information about the sites of disease which lead to the clinical stage was included in the CRFs. The site(s) of disease (Sites of Current Involvement) followed for progression could be used to document the clinical stage in one-hundred four cases. In twenty-two instances the clinical disease stage did not correspond with the lesions listed under the Sites of Current Involvement. (In Table I an asterisk indicates the number of times the stage reported did not match information in the CRF). An increased number of patients (seven) with liver metastases is noted on the FU arm. All other disease sites were equally represented in both arms.

Three patients on the gemcitabine arm had radiation therapy prior to initiation of drug. Likewise seven patients on the gemcitabine arm were reported to have excision of primary as compared to three patients on the FU arm.

Baseline clinical benefit response parameters (KPS, PI, and AC) will be discussed in the section which discusses Clinical Benefit Response Results.

Study Discontinuations Within the First Thirty Days:

Table 2 lists the number of patients who discontinued study within thirty days of randomization and the reason for study discontinuation.

Table 1: Patient Demographics

Parameter	Gemcitabine Arm	5-FU Arm
Sex		
Male	29 (46%)	29 (46%)
Female	34 (54%)	34 (54%)
Race		
African Descent	1 (1.1%)	5 (7.9%)
Caucasian	58 (92%)	53 (84.1%)
Asian	1 (1.6%)	0
Hispanic	3 (4.8%)	5 (7.9%)
Age		
Median	62	61
Range	(37-79)	(36-77)
Tumor Stage (Sponsor Data)		
II	9 (14.3%)	5 (7.9%)
III	9 (14.3%)	10 (15.9%)
IV	45 (71.4%)	48 (76.2%)
Disease Site		
Liver Metastases	31 (49.2%)	38 (60.3%)

Table 2: Discontinuation within Thirty Days of Randomization

Reason	Gemcitabine	5-FU
Objective Progression:	5	26
≤ 7 days on study	(-)	(4)
8 - 14 days on study	(-)	(1)
15 - 21 days on study	(2)	(4)
22 - 30 days on study	(3)	(17)
Clinical Progression	1	2
Drug Toxicity	2	1
Other: Diagnosis in Question		1
Pt. Refusal	1	
Gi Bleed	-	1
Pulmonary Emboli	1	1
Liver Failure	-	1
Coagulopathy	1	
Acute MI	1	
Total	12	33

More patients on the FU arm were discontinued within thirty days due to progressive disease. At day thirty fifty-one patient remain on study on the gemcitabine arm as compared to thirty on the FU arm. Study eligibility requirements included a life expectancy of 12 weeks, however, thirty-four patients died within the first twelve weeks of study. Of the three patients with clinical progression discontinued within thirty-days, one patient (255-3023-gemcitabine) _____ days after study removal. For the two patients on the FU arm, one patient (254-3168) was removed from study due to increased abdominal pain (This patient was a protocol violation since patient was placed on study with ascites.) and _____ days after study removal from disease progression and the second patient, 256-3225, on the FU arm, _____ after removal from study due to disease progression.

Time to Progression

Time to progression is defined in the protocol as time from randomization to time of study discontinuation or disease progression. For this review the time to progression is defined as the time from randomization to the time of objective tumor progression while on study. Patients who have progression after removal from study are considered as non-progressor for analysis. In review of the CRFs in several instances the patient was noted to have new onset of jaundice, new onset of ascites, or new disease sites on PE consistent with progression of disease. In all cases the patient had further evidence of progressive disease on the next CT scan. The date of progression assigned in this case was the date that first evidence of progression was noted in the CRF. Cases of "clinical progression" are censored from TTP analysis since objective evidence of progression is lacking.

In the time to progression analysis for this study ten patients on the gemcitabine arm and six patients on the FU arm were not evaluable for response. On the gemcitabine arm 11 patients were not evaluable for the following reasons: (1) patient refusal to continue therapy - 5; (2) clinical progression - 3; (3) death due to complications of disease progression - 1; (4) adverse drug reaction - 1, and (5) non-progression at censoring date - 1. On the FU arm twelve patients were not evaluated: (1) clinical progression - 8, (2) refusal to continue therapy - 2, (3) no progression at off-study date - 1, (4) liver failure not attributed to disease progression - 1 (In this patient disease progression was documented after study removal.)

Table 3: Time to Progression Analysis

Parameter	Gemcitabine N = 63	FU N = 63
No. Censored (%)	11 (17.5%)	12 (19%)
Median Time to Progression (Days) (Range - Days)	65 (0 - 288)	29 (0 - 365 +)
95% Confidence Interval	56 - 111	26 - 57
Risk Ratio (95% Confidence Interval)	0.53 (0.35 - 0.84)	
Log-rank p-Value	0.005	

An exploratory subset analysis of time to progression for patients on study more than thirty days is presented. This exploratory subset analysis was done due to the much larger number of drop-outs on the FU arm as compared to the gemcitabine arm.

Table 4: Time to Progression, Patients on Study > 30 Days

Parameter	Gemcitabine N = 47	FU N = 30
Censored (%)	10/47 (21.3%)	9/30 (30.5%)
Median (Days) (Range in Days)	78 (0 - 288)	64 (0 - 365+)
95% Confidence Interval (Days)	57 - 120	59 - 109
Risk Ratio (95% Confidence Interval)	0.87 (0.51 - 1.50)	
Log Rank p-value	0.61	

In this exploratory subset analysis no difference in time to progression is detected between the two arms for those patients who remained on study after the first thirty days.

Time to Treatment Failure

Time to treatment failure is defined as the time from randomization until the time that a patient goes off study for tumor progression, worsening clinical symptoms (clinical progression), adverse events, refusal to continue treatment, or death. Patients who complete therapy and are taken off study with a complete or partial response are not counted as treatment failures. One patient on the FU arm is a nonprogressing responder at off-study date and is censored as are two nonprogressing responder on the gemcitabine arm.

Table 5: Time to Treatment Failure

Parameter	Gemcitabine N = 63	FU N = 63
No. Censored	2 (3.2%)	1 (1.6%)
Median Time Treatment Failure in Days (Range in Days)	56 (0-288)	27 ((0-365+))
95% Confidence Interval (Days)	40-71	25-31
Risk Ratio (95% Confidence Interval)	0.56 (0.39 - 0.81)	
Log Rank p-value	0.001	

Note that the time to treatment failure is significantly shorter in the FU arm as compared to the gemcitabine arm and reflects the large number of dropout on the FU arm as compared to the gemcitabine arm in the first thirty days.

Survival

Survival by treatment arm is shown in the following table:

Table 6: JHAY-Survival by Arm

Parameter	Gemcitabine N = 63	FU N = 63
No. Censored (%) (Alive at Last Follow-Up)	8 (16.3%)	1 (4.2%)
Median Survival Time in Days (Range in Days)	173 (0-538)	129 (0-460)
95% Confidence Interval in Days	(146-210)	(98-156)
Risk Ratio (95% Confidence Interval)	0.53 (0.36-0.77)	
Log Rank p-value	0.0008	

The median survival for the gemcitabine of 173 days or 24.7 weeks is slightly greater than the survival time reported for FU in the literature (~ 22 weeks). The survival time for patients treated with FU on this study is markedly less (> 4 weeks) than that reported in the literature. An

exploratory subset analysis was performed on patients on study for more than 30 days to explore effect on survival when the large number of dropouts on the FU arm within the first 30 days due to disease progression. The following table presents these results:

Table 7: Survival, Patients on Study > 30 Days

Parameter	Gemcitabine (N = 51)	FU (N = 30)
No. Censored (%)	7	1
Median Survival Time, Days (Range - Days)	175 (0 - 538)	177 (0 - 460+)
95% Confidence Interval	159 - 234	148 - 214
Risk Ratio (95% Confidence Interval)	0.68 (0.42 - 1.11)	
Log Rank, p-value	0.12	

When these two groups are compared, no difference in survival is detected. The subset survival time (25 weeks) on both arms is similar and survival is somewhat greater than that reported in the literature for FU (22 weeks).

Objective Response Rates:

Response rates are based on evaluation of information in the CRFs. Radiological reports to document the tumor measurements were not included in the CRFs. In some instances the original measurements were crossed out and the response changed. In one instance (254-3164) the EV notation was crossed out and 0 substituted for the measurements. Numerous written notations were included where PR vs. CR were discussed. The reviewer's overall assessment of this situation is the responses are non-evaluable. In several instances the tumor measurements in the CRF did not support the notation of progressive disease. Table 8 reports the responses as judged from the case report forms.

Table 8: Response Rates (Based on CRF Data)

Response Category	Gemcitabine No. (%)	FU No. (%)
Complete	-	1 (1.6)
Partial	2 (3.2)	1 (1.6)
Stable	25 (39.7)	15 (23.8)
Progressive	24 (38.1)	40 (63.5)
Non-Evaluable	12 (19.0)	6 (9.5)

Some patients remained on study with progressive disease by tumor measurement. Review of Table II in the appendix will indicate where the reviewer and the sponsor differ as to response and the reason for the discrepancy is given in the comment section. An External Oncology Review Board, sponsored by Eli Lilly consisting of two radiologists and an oncologist, reviewed twelve patient's radiographic

data. This panel found no responses in any of reviewed cases. No information was included in the NDA as to which cases were examined and the reasons for the panel's judgement . The protocol did not specify that the same "cuts" on CT or MRI **must be used** but suggested that the cuts be similar. Based on the information in the case report forms the response (CR + PR) rate in each arm is 3.2% (2/63). Internal review of scans and ultrasounds confirmed partial responses in two patients on the FU arm in JHAY, none on the gemcitabine arm.(See Table V in the Appendix.)

Clinical Benefit Response Analysis:

Baseline CBR parameters are presented in the following table. Along with investigator site, pain intensity (PI), analgesic consumption (AC), and performance status (KPS) were stratification factors.

Table 9: Baseline Clinical Benefit Response Parameters

Parameter	No. Gemcitabine Arm (%)	No. FU Arm (%)
Performance Status		
50	2 (3.2)	1 (1.6)
60	9 (14.3)	8 (12.9)
70	33 (52.4)	34 (54.8)
80	11 (17.5)	13 (21.0)
90	8 (12.7)	6 (9.7)
Unspecified	0	1
Pain Intensity		
0 - 10	10 (15.9)	10 (15.9)
11 - 20	12 (19.0)	15 (23.8)
21 - 30	12 (19.0)	9 (14.3)
31 - 40	12 (19.0)	11 (17.5)
41 - 50	9 (14.3)	10 (15.9)
51-100	8 (12.7)	8 (12.7)
Analgesia Consumption		
0 - 50	19 (30.2)	18 (28.6)
51 - 100	21 (33.3)	18 (26.8)
101 - 150	9 (14.3)	10 (15.9)
151 - 200	10 (15.9)	8 (12.7)
201 or >	4 (6.3)	11 (17.5)

The initial randomization strata were defined as: 1) pain intensity (baseline score ≥ 30 or < 30); 2)

analgesic consumption (baseline score ≥ 60 mg morphine equivalents or < 60 mg morphine equivalents); 3) performance status (baseline KPS ≥ 70 or ≤ 60). Randomization was dynamically allocated. The stratification criteria were amended on February 25, 1994 as follows: pain intensity (baseline score ≥ 20 or < 20), analgesia consumption (baseline score ≥ 10 or < 10), performance status (baseline KPS ≥ 80 or ≤ 70). The applicant's justification for change in CBR strata was as follows: "Change in the cut-off values would allow for baseline values which would provide a better 50/50 split between high and low strata for each prognostic factor." Since one hundred thirty-six possible stratification combinations existed and only one hundred twenty-six patients were enrolled in the study using dynamic randomization imbalance between arms was possible (too few patients to fill all the strata). Imbalance in the analgesic consumption scores is an example of this. Seven more patients with a high analgesic consumption (greater than 201 mg. morphine equivalents/day) were enrolled on the FU arm. With regard to PI and KPS the distribution is more equal between the two groups.

By definition the number of patients eligible for clinical benefit response is lower than the number of patients available for assessment of objective response parameters. Fifty-two patients were on the gemcitabine arm for greater than four weeks, and thus eligible for clinical benefit response (Primary components had to be stable or positive for four weeks.) On the FU arm forty-three patients were eligible for clinical benefit response evaluation. The following table shows the distribution of the primary clinical response parameters by arm where a positive or stable designation has the potential for response.

Table 10: Clinical Benefit Response by Arm

Gemcitabine (N = 52)			Pain Intensity and/or Analgesia Consumption	FU (N = 43)		
Performance Status				Performance Status		
Positive	Stable	Negative		Positive	Stable	Negative
4 (7.8%)	10 (19.6%)		Positive	1 (2.3%)	2 (4.6%)	1 (2.3%)
	15 (28.4%)		Stable		18 (41.9)	
4 (7.8%)	18 (35.3%)	1 (1.96%)	Negative	2 (4.6%)	18 (41.9%)	1 (2.3%)

(Shaded areas = CBR; One applicant designated responder removed due to missing data)

In reviewing the CBR results, the CBR designation for one responder (249-3130) on the gemcitabine arm is challenged hence the reviewer reports only fourteen CBRs. While this patient had decreases in PI and AC for week 8 - 11 to 50% of baseline, KPS scores for the patient were missing on weeks 4, 6, 9, 13 so that four consecutive weeks of stable PS were not present at time of clinical benefit response designation. Table III in the appendix describes the objective tumor response, the CBR, and comments about the clinical course of each of the CB responders. Fifteen clinical benefit responses were reported in the gemcitabine arm and three in the FU arm. Parameters on which the clinical benefit response designation was achieved are listed below:

Pain Intensity, AC, and KPS.....	1
Pain Intensity and AC.....	8
Pain Intensity.....	4
Pain Intensity and PS.....	1
AC.....	1
AC + KPS.....	1
PS.....	1

Four patients on the gemcitabine arm, achieved clinical benefit response solely on the basis reduction of pain intensity (a subjective measure). All achieved CBR at the end of the first four weeks of the trial. Benefit was sustained for six to twelve weeks in these patients. The time at which clinical benefit was achieved for all responders is shown below:

Table 11: Time of Clinical Benefit Response Attainment

Time on Study	Gemcitabine	FU
≤ 4 weeks	7	2
5-8 weeks	2	-
9-12 weeks	3	-
≥ 12 weeks	2	1

The duration of clinical benefit response is shown in the following table:

Table 12: Duration of Clinical Benefit Response

No. of Weeks	Gemcitabine (N=14)	FU (N=3)
≤ 4 weeks	-	-
4 - 8 weeks	4	1
9 - 16 weeks	2	2
17 - 24 weeks	2	-
25 - 32 weeks	5	-
≥ 33 weeks	1	-

For most patients clinical benefit response, if it occurred, occurred during the first twelve weeks of study. Duration of clinical benefit response designation is much longer on the gemcitabine arm, however the pool of patient's on the FU arm available for the CBR designation was much smaller due to the large number of drop-outs in the first four weeks.

Clinical benefit response does not appear to correlate well with objective tumor response as

demonstrated in the following table.

Table 13: Clinical Benefit Response vs. Tumor Response

Objective Response	Gemcitabine Arm N=14	FU Arm N=3
Complete	—	1
Partial	2	—
Stable	8	2
Progression	3	—
Non-Evaluable	1	—

Seven of the fourteen clinical benefit responders on the gemcitabine arm received full dose of drug on schedule with escalation as planned per protocol. Seven could not tolerate the dosing schedule. Two of three FU clinical benefit responders received full FU dose on schedule. About half of the clinical benefit responders developed drug related toxicities resulting in reduction and/or delay in dose. Most toxicities were grade 1-2, however, two patients developed moderate to severe anemia, one hemolytic in nature and one of unclear etiology. One patient on the gemcitabine arm refused further therapy after he developed several drug related toxicities.

Repeated measures analysis on the parameters of clinical benefit was performed by the applicant and included in the NDA submission. The slope from a simple linear regression line for each patient was obtained for each clinical benefit response variable (PI, AC, PS, and weight). These variables were stratified by 4-week time intervals. Wilcoxon rank-sums were computed and standardized to provide the test statistics for treatment differences within strata. A weighted sum of the within strata test statistics was computed to provide for an overall test statistic. Both right-tailed and left-tailed p-values were presented for treatment comparisons within group with regard to the overall test statistic. Of note, the left-tailed p-value is pertinent to the analysis of pain and analgesic consumption, while the right-tailed p-value is pertinent to the overall statistics for KPS and weight. In the analysis no statistically significant difference was found between the gemcitabine arm and the FU arm in any analysis. With regard to the means within the strata for pain intensity and analgesia consumption, the means tended to favor gemcitabine over FU but were not significantly significant..

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Deaths:

Four patients died on study. No deaths were drug related.

Hospitalizations:

Sixty-eight hospitalizations involving approximately fifty patients occurred during this trial. The

majority of these hospitalizations were related to the underlying disease process. Forty-six hospitalizations occurred in the gemcitabine arm, fourteen in the FU arm (eight hospitalizations occurred at time of study entry and are not considered further). Sixteen hospitalizations are judged to be therapy related. The reason for the drug related hospitalization on each study arm are listed in the following table.

Table 14: Drug Related Hospitalizations

Reason	Gemcitabine	FU
Nausea and Vomiting	6	3
Infections-Cellulitis with Neutropenia	1	-
Fever	1	-
Anemia	1	
Dyspnea	1	
Infectious Diarrhea		1
Anxiety	2	

On the gemcitabine arm six patients were hospitalized with eight episodes of deep venous thrombosis and two patients were hospitalized with one episode of superficial thrombophlebitis. On the FU arm three patients required hospitalization for treatment of DVT. Two patients, one on each arm, had coagulopathy associated with disease. In one patients (271-3299) death due to multiple venous and arterial occlusions after the first injection of gemcitabine. The coagulopathy was reported to be difficult to control prior to entrance on study and relationship to administration of study drug is unclear.

Study Discontinuations

Seventeen patients discontinued study due to an adverse event. Six were related to drug, five on the gemcitabine arm and one on the FU arm. Table IV in the appendix discusses each case. Individual cases will be mentioned as indicated in the appropriate toxicity section.

Adherence to Dose Assignment and Schedule;

Thirty-three of the sixty-three patients (52.4%) assigned to gemcitabine completed all seven injections in the first cycle of therapy with twenty-one patients continuing on study to receive a second cycle of therapy. Of the thirty patients who did not complete all seven first cycle injections, twelve continued into the second cycle. On the FU arm thirty-nine of the sixty three patients (61.2%) received the first four injections on schedule. Twenty-three patients continued on to the second cycle of FU therapy. Of the twenty-four patients who received less than four injections, two went on to start a second cycle.

Table 15 provides information about variations in the amount of dose delivered per injection number.

Table 15: Dosing Information

	Gemcitabine (%)	FU (%)
Total No. of Injections	692 (100)	483 (100)
Actual No. Administered	634 (91.6)	439 (90.8)
Administered as Assigned	403 (58.2)	344 (69.2)
Escalated Doses	69 (13.9)	79 (16.4)
Reduced Doses	135 (19.5)	26 (5.4)
Omitted Doses	58 (8.4)	44 (9.1)

More doses were administered as assigned (including escalations) and fewer dose reductions occurred on the FU arm. The reasons given for the dose omissions include thirty myelosuppressive events on the gemcitabine arm. On the FU arm, nausea was the reason given for four dose omissions, diarrhea for six, and thrombocytopenia for one. Other reasons for dose omissions include other adverse events, missed clinic visits, or disease progression.

The reason for dose reduction is difficult to determine: reason for dose reduction was not always indicated by the investigator; dose reduction continued once toxicity cleared with no reescalation; On the gemcitabine arm forty-one dose reductions were known to be due to leukopenia, thirty-six due to thrombocytopenia, two for anemia, three for diarrhea, and one for rash. On the FU arm leukopenia was responsible for one dose reduction, thrombocytopenia for nine, and fever for one.

Treatment Related Signs and Symptoms Reported on Study:

The following table reports the Treatment-Emergent Signs and Symptoms (TESS) for this study. Note that discrepancies occur in the numbers of patients reported with a particular symptom between this data base and the WHO Toxicity Grading data. A particular sign or symptom did not always receive a toxicity grade after the first cycle in the WHO grading. Some symptoms were reported more than once using a different classification term. Problems were encountered in trying to discern if a particular toxicity was related to drug or worsening of the underlying disease process. By use of separate grading scales to delineate between what were disease-related symptoms and what were treatment related symptoms, the sponsor tried to provide a more accurate assessment of toxicity, sometimes without success.

Table 16: Treatment Emergent Signs & Symptoms

Toxicity	Gemcitabine N=63 (%)	FU N=63 (%)
Asthenia	40 (63.5)	30 (47.6)
Allergic Rx.	1 (1.6)	-
Fever	30 (47.6)	16 (25.4)
Serious	1	-
Neutropenic	1	-
Septic	2	-
Flu Syndrome	10 (15.9)	5 (7.9)
Nausea	44 (71.0)	41 (65.1)
Severe	3	3
Vomiting	33 (53.2)	33 (54.0)
Severe	6	2
Diarrhea	26 (41.3)	21 (33.3)
Edema	7 (11.1)	4 (6.3)
Generalized	1 (01.6)	1 (01.6)
Peripheral	25 (39.7)	13 (20.6)
Dyspnea	11 (17.5)	9 (14.3)
Malignant Involvement	1	2
Increased Cough	11	3
Malignant Involvement	1	1
Pleural Effusions	7	10
Malignant	2	2
Rash	16 (25.4)	6 (14.3)
Alopecia	11 (7.5)	10 (15.9)
Amblyopia	4 (6.3)	1 (1.6)
Taste Perversion	4 (6.3)	4 (6.3)

Generalized edema associated with gemcitabine treatment has been reported. Etiology is unclear. Diuretics can be used to treat symptomatic edema. One patient (265-32260) was hospitalized due to severe lower extremity edema considered drug induced (Doppler negative). One patient (250-3042) from study due to dyspnea related to study drug. Dyspnea which occurs within twenty-four hours of gemcitabine administration is usually transient and of unclear etiology. Dyspnea occurred in about 10% of the patients and one patient discontinued treatment due to severe dyspnea following treatment.

Forty-seven per cent of the patients on the gemcitabine arm had the constellation of headache, fever, chills, sometimes with myalgias. This flu-like syndrome can last for 2-7 days. No patients discontinued study due to the flu-like syndrome. One patient (250-3050) discontinued study due to a

maculopapular rash which worsened with each subsequent injection despite antihistamine therapy. No cases of exfoliative dermatitis (grade 3) were reported.

WHO Toxicity Grading of Specific Toxicities:

To appreciate the toxicity profiles of the study drugs, FU and gemcitabine, WHO toxicity grading for pertinent toxicities is presented in the following tables. Toxicity by cycle will not be reported since the cycle lengths are not comparable.

Table 17: Hematologic Toxicities

Parameter	Gemcitabine Arm (%) N=63	FU Arm (%) N=63
Leukopenia	30 (47.6)	3 (4.8)
Granulocytopenia		
Gr. I	6 (10.3)	4 (6.5)
Gr. II	15 (25.9)	4 (6.5)
Gr. III	11 (19.0)	1 (1.6)
Gr. IV	4 (6.9)	2 (3.3)
Absolute Granulocyte Count		
≥ 500/ul	54 (85.7)	60 (95.2)
≤ 500/ul, < 7 days	4	1
≤ 500/ul, ≥ 7 days	1	1
Neutropenic Fever	1	-
Neutropenic Sepsis	1	-
Thrombocytopenia		
Gr. I	26 (30.6)	6 (9.5)
Gr. II	13 (21.0)	1 (1.6)
Gr. III	6 (9.7)	1 (1.6)
Gr. IV	-	-
Anemia		
Gr. I	19 (30.6)	17 (27.4)
Gr. II	15 (24.2)	11 (17.7)
Gr. III	4 (6.5)	-
Gr. IV	2 (3.2)	-
No. RBC Transfusions	17 (27)	5 (7.9)

Review of this data indicates that gemcitabine is more myelosuppressive than FU. Prolonged granulocytopenia and increased incidence of sepsis are not seen. Thrombocytopenia occurred with greater frequency with gemcitabine usage and resulted in dose reduction/omission with no increased incidence of bleeding due to low platelet counts. Anemia was more severe on the gemcitabine arm. Three patients, all clinical benefit responders, had problems with Gr. III/IV anemia. One patient (254-3162) developed proteinuria, hematuria, thrombocytopenia, required transfusion of eight unit PRBCs, and received Prednisone 40 mg/day to treat anemia. The patient was removed from study to "disease progression", but at the time of study removal, had not received study drug for seven weeks. The second patient (255-3306) had a history of hemochromatosis, possibly a history of alcohol abuse,

many gemcitabine dose reductions and omissions, a decrease in hemoglobin from 12.9 gm% (study entry) to 6.2 gm% (study discontinuation). Preexisting hepatic dysfunction along with small amount of study drug appear to account for the development of the grade IV anemia. A third patient (271-3297) required transfusion of two units of packed RBCs for a 2 Gm. drop in hemoglobin thirteen days after study initiation not explained by Gi bleeding.

Renal toxicity grading is presented in the following table.

Table 18: Renal Toxicity

Parameter	Gemcitabine	FU
Proteinuria (Gr.I)	6 (6.3)	1 (1.6)
Hematuria (Gr. I)	9 (14.3)	-
Creatinine Elevation (Gr. I)	1	-

No patients were removed from study due to renal toxicity. The etiology of grade 1 proteinuria and grade 1 hematuria is unclear. In the phase II studies decreased renal function was reported in three patients associated with hematuria and proteinuria.

Table 19 describes the abnormalities of the grading in liver function.

Table 19: Hepatic Toxicity

Parameter	Gemcitabine Arm N=63	FU Arm N=63
Alkaline Phosphatase Elevations	10 (16.4)*	25 (39.7)*
ALT Elevations		
Gr. II	18 (29.5)	14 (14.3)
Gr. III	5 (8.6)	-
Gr. IV	1 (1.6)*	-
AST Elevations		
Gr. II	12 (19.7)	15 (23.8)
Gr. III	6 (9.8)	1 (1.6)*
Gr. IV	1 (1.6)	-

* Elevation documented to be due to disease in all cases.

Gemcitabine treatment is associated with transient elevation of ALT and AST (Gr.1 or 2) which usually occur in the first four weeks of therapy. Dose reduction were required on a few occasions in this trial for abnormal LFTs, but no patient was removed from study due to drug related hepatic toxicity alone. In two patients (255-3021, 258-3254) abnormal liver functions associated with other toxicities resulted in study discontinuation.

Gastrointestinal Toxicities are shown in Table 20.

Table 20: Gastrointestinal Toxicities

Parameter	Gemcitabine Arm N=63 (%)	FU Arm N=63 (%)
Nausea and Vomiting		
None	23 (36.5)	26 (41.9)
Gr. I	18 (28.6)	16 (25.8)
Gr. II	14 (22.2)	17 (27.4)
Gr. III	6 (9.5)	3 (4.8)
Gr. IV	2 (3.2)*	
Diarrhea		
None	48 (76.2)	43 (69.4)
Gr. I	11 (17.5)	9 (14.5)
Gr. II	3 (4.8)	7 (11.3)
Gr. III	1 (1.6)	3 (4.8)**
Mucositis		
None	54 (85.7)	53 (85.5)
Gr. I	7 (11.1)	8 (12.9)
Gr. II	2 (3.2)	1 (1.6)

* One case due to disease related obstruction.

**One case related to C. difficile enterocolitis.

Patients received antiemetic while on study. Many patients had nausea and vomiting due to their underlying disease state, therefore quantitation of the frequency/severity of vomiting due to study drug is impossible. Gemcitabine does cause more nausea and vomiting than FU. In four patients (255-3021, 250-3041, 254-3021, 258-3254) three on gemcitabine and one on FU nausea and vomiting were given as a reason for study discontinuation. More cases of diarrhea of greater severity were reported on the FU arm. The incidence of mucositis (Gr. I/II) is the same on both arms.

Other Toxicities

No allergic reactions were reported. Mild alopecia (Gr. 1) occurred in about 10% of patients. Peripheral neuropathy (Gr. 1) was reported in one patient on each arm. Somnolence was reported, but what role if any drug may play is unclear.

Study Summary

One hundred twenty-six patients, after a two to seven day lead-in period to allow for pain stabilization, were randomized to treatment with either gemcitabine or FU in a single blinded trial. Patients were well matched on each arm for sex, age, race, stage, and performance status. Seven more patients on the FU arm had liver metastases. Seven more patients were taking greater than 200 mg morphine equivalents on the FU arm. At thirty days: twelve patients had discontinued study in the gemcitabine arm and thirty-three patients in the FU arm.

The primary endpoint of this study was clinical benefit response, a composite based on improvement and/or stabilization of pain intensity, analgesia consumption, and performance status. Fourteen patients in the gemcitabine arm and three patients in the FU arm had clinical benefit responses lasting from six to thirty-five weeks. The objective response rate in each arm was 3.2%, although no responses were confirmed by an Eli Lilly sponsored external review board. Median time to progression was 65 days on the gemcitabine arm (range: 0 - 288 days) and 29 days (range: 26 - 365+) on the FU arm (Log rank p-value: 0.005). Median time to treatment failure on the gemcitabine arm is 56 days (range: 0-288 days) and 27 days (range: 25- 365 + days) on the FU arm (Log-rank p value: 0.001). Median survival was 173 days (range: 146-210 days) on the gemcitabine arm and 129 days (range: 98-156 days) on the FU arm (Log-rank p-value: 0.0008).

Toxicities reported on the gemcitabine arm include: asthenia -63.5%, fever -47.6%, flu-syndrome -15.9%, nausea -71%, vomiting -53.2%, diarrhea -41.3%, edema 11- 39%, and rash -25%. On the FU arm toxicities include: asthenia -47.6%, fever -25.4%, flu syndrome -7.9%, nausea -65.1%, vomiting-54%, diarrhea -33%, edema 6 - 20%, and rash-14.3%. Laboratory toxicities include neutropenia, thrombocytopenia, and anemia and were increased in frequency on the gemcitabine arm, with some patients having Gr. 3,4 anemia and neutropenia. AST and ALT were more often elevated on the gemcitabine arm during the first two-three cycles of therapy, but these elevations resolved in later cycles. Alkaline phosphatase was often elevated but due to tumor infiltration of the liver so no generalizations about gemcitabine induced alkaline phosphatase elevations can be made. Hematuria and proteinuria without elevation of serum creatinine were reported on the gemcitabine arm.

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Table 1: JHAY- Patient Data Base

No.	Study Number	Rx.	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
1	201-3301	G	4*	12-21-93	02-17-94	02-17-94	OP	—	Disease
2	206-3001	F	4*	09-10-92	10-05-92	10-05-92	OP	—	Disease
3	206-3002						INELIGIBLE — Elevated LFTs	—	Disease
4	206-3003	F	3	01-19-93	11-02-93*	02-28-94	OP	—	Disease
5	206-3004	F	4	01-28-93	04-21-93*	05-19-93	OP	—	Disease
6	206-3005	G	2	02-04-93	03-02-93	03-18-93	OP	—	Disease
7	206-3006						INELIGIBLE — Inadequate BM reserve	—	Disease
8	206-3007						INELIGIBLE — Active Infection	—	Sepsis
9	206-3008	F	4	04-01-93	04-28-93	04-28-93	OP	—	Disease
10	206-3009	F	3	04-15-93	05-13-93	05-13-93	OP	—	Disease
11	206-3010	F	4	07-01-93	10-21-93	10-28-93	OP	—	Disease
12	206-3011	G	4	11-22-93	12-27-93	12-27-93	OP	—	
13	206-3012	G	4	03-08-94		05-17-94	PLR refusal-Worsening heart failure on treatment	—	
14	210-3081	G	2*	08-26-92	01-06-93	01-13-93	OP	—	Disease
15	210-3082	G	4	09-30-92	01-27-93*	02-03-93	OP	—	Disease
16	210-3083	F	4	10-26-92	10-28-92*	11-18-92	OP (Developed ascites)	—	Disease
17	210-3084	F	4	11-23-92	12-18-92	12-18-92	OP	—	Disease
18	210-3085	G	4	08-02-93	—	08-04-93	Acute inferior MI — PT refused further Rx after MI	—	Disease
19	210-3086	F	4	09-23-93	10-19-93	10-21-93	OP	—	Disease
20	210-3087	F	4	01-18-94	02-11-94	02-11-94	OP	—	Disease
21	210-3088	F	2*	02-07-94	—	06-24-94	CP	—	Disease
22	213-3141	G	4	01-29-93	03-22-93	03-23-93	OP	—	Disease
23	213-3142	G	2*	06-01-93	—	11-22-93	CP	—	—
24	213-3143	F	2*	06-15-93	—	09-28-93	CP	—	Disease
25	213-3147	F	4	10-29-92	—	11-16-92	(Increased bilirubin due to stent obstruction after one dose of FU); Objective progression (off-study)	—	Disease

OP means progression documented objectively; Clinical progression means patient clinical condition is deteriorating with objective demonstration of increase in tumor burden.

* Asterisk indicates disagreement between reviewer and sponsor in this area

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Table 1: Patient Data Base

No.	Study Number	Drug	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
26	219-3181	F	4	09-15-92	10-27-92*	11-18-92	OP	—	Disease
27	219-3183	F	4	09-30-92	—	10-22-92	—	—	Pulmonary Emboli
28	219-3189	G	3*	11-13-92	01-11-93	01-14-93	OP	—	Disease
29	219-3185		4				Ineligible Pt. refused		
30	219-3187	F	4	10-16-92	11-10-92*	11-13-92	OP	—	Disease
31	219-3188	F	4	11-04-92	11-30-92*	12-09-92	OP	—	Disease
32	219-3190	G	4	11-17-92	01-12-93	01-20-93	OP	—	Disease
33	219-3191						Ineligible Pain not stabilized		
34	219-3192	G	4	12-09-92	—	06-03-93	Pt. refusal: Side effects of drug intolerable	—	Disease
35	219-3193	G	3*	02-16-93	05-04-93	05-06-93	OP	—	Disease
36	219-3194	G	4	02-16-93	03-08-93	03-08-93	OP	—	Disease
37	219-3195	G	4	02-18-93	03-18-93*	04-12-93	OP	—	Disease
38	219-3196	F	4	02-23-93	03-23-93*	04-12-93	OP	—	Disease
39	219-3197	G	4	04-05-93	04-27-93*	06-03-93	OP	—	Disease
40	219-3198	G	4	04-28-93	06-30-93	07-08-93	OP	—	Disease
41	219-3199	F	3	07-26-93	11-15-93	01-10-94	OP	—	Disease
42	219-3200	F	4	08-09-93	08-30-93	09-29-93	OP	—	Disease
43	219-3286	G	4	08-17-93	10-20-93	11-18-93	OP	—	Disease
44	219-3287	G	4	09-14-93	11-09-93	11-18-93	OP	—	Disease
45	219-3288	G	4	10-12-93	11-10-93	11-11-93	OP	—	Disease
46	219-3289	F	4	01-12-94	01-17-94	02-02-94	OP	—	Disease
47	219-3290	G	4	01-14-94	—	02-21-94	Adverse Event: GI bleed, ? disease related	—	Disease
48	219-3321	F	2*	01-24-94	03-28-94	04-12-94	OP	—	Disease
49	219-3322	F	4	03-22-94	04-19-94	04-19-94	OP	—	Disease
50	242-3281	G	4	01-19-94	03-15-94	03-15-94	OP	—	Disease

Appendix: JHAY
Table I: JHAY - Patient Data Bay

No.	Study Number	Rx	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
51	249-3121	F	4	11-19-92	01-14-93	01-14-93	OP	—	Disease
52	249-3122		4				Ineligible: Unable to tolerate Vena puncture	—	Disease
53	249-3123	G	2	01-19-93	03-16-93	03-17-93	OP	—	Disease
54	249-3124	G	4	02-24-93	04-20-93	04-20-93	OP	—	Disease
55	249-3126	F	2*	04-08-93	06-08-93*	08-22-93	OP	—	Disease
56	249-3127	G	4	06-01-93	07-20-93	08-27-93	OP	—	Disease
57	249-3128	F	2	10-12-93	11-04-93	11-08-93	OP	—	Disease
58	249-3129	F	4	11-08-93	01-04-94	01-04-94	OP	—	Disease
59	249-3130	G	2*	11-15-93	—	03-21-94	(Pt. refused further treatment)	—	—
60	249-3327	G	4	01-31-94	—	—	(On Study: 09-06-94)	—	—
61	250-3041	F	4	10-08-92	—	11-05-92	(Pt. refused further treatment due to severe chemo-induced nausea)	—	Disease
62	250-3042	G	4	11-12-92	—	12-09-92	(Adverse Rx: Pt. developed severe dyspnea following each treatment)	—	Disease
63	250-3043	G	4	12-21-92	06-11-93	06-17-93	OP	—	Disease
64	250-3044	F	2*	12-29-92	01-14-93	01-19-93	OP	—	Disease
65	250-3045	F	4	01-07-93	01-27-93	06-21-93	OP	—	Disease
66	250-3046	F	4	01-18-93	02-10-93	02-10-93	OP	—	Disease
67	250-3048	G	2*	02-23-93	04-15-93	06-17-93	OP	—	Disease
68	250-3049						Ineligible: Severe COPD	—	Disease
69	250-3050	G	4	08-05-93	—	08-19-93	Adverse Rx: Severe Rash, Allergic	—	Disease
70	250-3052	G	3	03-23-94	04-14-94	04-20-94	OP	—	—
71	250-3053						Ineligible: Ascites	—	Disease
72	251-3201	F	2	10-13-92	—	12-10-92	Clinical Progression, Disease Stable	—	Disease
73	251-3202						Ineligible: Abnormal LFTs	—	Disease
74	251-3203	G	4	07-05-93	—	07-19-93	Clinical Progression, developed hep failure, Rx related	—	Disease
75	251-3209	F	2	01-10-94	—	02-14-94	Pt. refused, decrease in quality of life with treatment	—	Disease

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Table 1: JHAY - Patient Data Base

No.	Study No.	Rx.	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
76	251-3205		4				Ineligible - Lack of pain stabilization		Disease
77	251-3206	G	4	11-15-93	12-14-93*	03-28-94	OP		Disease
78	251-3207	F	4	11-15-93	12-13-93	12-13-93	OP		Disease
79	252-3061	G	4	11-25-92	06-29-93	08-24-93	OP		Disease
80	252-3062	F	4	10-14-93	---	03-15-94	CP		Disease
81	252-3063	F	4	11-18-93	01-12-94	01-12-94	OP		Disease
82	253-3101	F	4	07-22-92	08-10-92	08-10-92	OP		Disease
83	253-3102	G	4	07-22-92	11-09-92	11-13-92	Gastrointestinal Bleed, CT progression		Disease
84	253-3104	F	4	08-19-92	09-02-92	09-14-92	Hepatic Failure, ?Drug		Liver Failure
85	253-3105						Ineligible - Abnormal LFTs		Disease
86	253-3106	G	4	09-02-92		09-23-92	Pt. refusal-Pt. wishes alternative therapy		Disease
87	253-3107				"		Ineligible - Abnormal LFTs		
88	253-3108	G	4	10-21-92	11-17-92	12-09-92	OP		Disease
89	254-3161						Ineligible - Abnormal LFTs		
90	254-3162	G	4	04-28-93	11-08-93	02-10-94#	Drug toxicity: Severe Anemia, HBP, thrombocytopenia, hematuria, proteinuria		Disease
91	254-3163	G	3	11-10-92	---	07-13-93	"Satisfactory Response" - Progression		Disease
92	254-3164	F	2	05-20-93	---	05-19-94	"Complete Response"		
93	254-3165		4				Ineligible - Abnormal LFTs		
94	254-3166	F	?	05-27-93		06-04-93	Dx in question		?
95	254-3167						Ineligible - Abnormal LFTs, Pt refusal to be on study		
96	254-3168	F	4	06-04-93		06-08-93	Pt. had increase in pain, thought have clinically progressed, Protocol violation (ascites on entry)		Disease
97	254-3169	F	3	07-12-93	---	09-07-93	Removed due to lack of efficacy with stable disease		Disease
98	254-3170						Ineligible - Abnormal LFTs		
99	254-3171						Ineligible - Dx in question		
100	254-3173	G	2	09-08-93	03-18-94	03-25-94	OP		

Patient did not receive study drug after 12-23-94.

Appendix 1:

Table 1: JHAY - Patient Data Base

No.	Study Number	Drug	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
101	254-3174	F	4	09-08-93		09-23-93	Death: GI Bleed		GI bleed
102	254-3176	G	4	10-11-93	---	03-30-94	CP		Disease
103	254-3177	F	2*	11-30-93	03-07-94*	04-25-94	P		Disease
104	254-3178	G	4	12-03-93	02-21-94*	05-18-94	OP		Disease
105	254-3179	G	4	02-09-94	---	03-20-94	Cerebral infarction		Disease
106	254-3180	F	4	03-16-94	03-19-94	03-28-94	jaundice; biliary obstruction		Disease
107	256-3021	G	4	08-17-92	---	10-14-92	Pt. refusal: Gr 4 vomiting		Disease
108	255-3022	G	4	09-14-92	02-23-93	02-23-93	OP		Disease
109	255-3023	G	4	11-10-92		12-01-92	Pt. refusal: Severe asthenia		Disease
110	255-3024		4				Ineligible/ Inadeq. BM reserve		Disease
	255-3025						Ineligible/ Abnormal LFTs		Disease
112	255-3026	F	4	07-15-93	08-03-93	08-12-93	OP		Disease
113	255-3027	G	2*	08-09-93	09-29-93*	11-16-93	Pt. Refusal: Worse symptoms with Rx.		Disease
114	255-3028						Ineligible/ Inadequate pain stabilization		GI Bleed
115	255-3029	F	4	09-07-93	---	10-26-93	Physician perception progression; objectively stable		Disease
116	255-3030	F	2*	09-20-93	10-13-93	10-15-93	OP		Disease
117	255-3031	F	2	11-24-93	12-20-93	12-21-93	OP		Disease
118	255-3032	F	2*	11-23-93	03-11-94	03-15-94	OP		Disease
119	255-3033	G	2*	01-10-94	---	01-27-94	Pulm. Emboli		Respiratory Failure-PTB
120	255-3034	F	4	01-10-94	03-02-94	04-04-94	OP		Suicide
121	255-3035		4				Ineligible/ Elevated		
122	255-3036	F	4	01-27-94	02-02-94*	02-22-94	GI Bleed with DIC due to Disease		Disease
123	255-3037	F	4	03-03-94	06-17-94*	06-18-94	OP		Disease
124	255-3038	G	2*	03-17-94	06-15-94	06-20-94	OP		Disease
125	255-3306	G	4	10-12-93	---	05-17-94	Clinical Progression		Disease

Appendix 1: JHAY

Table I: JHAY - Patient Data Base

No.	Study Number	Rx	Stage	Date of Randomization	Date of Progression	Date Off-Study	Reason for Study Discontinuation	Date of Death	Cause
126	255-3307	F	4	10-18-93	11-08-93	11-08-93	OP		Disease
127	255-3308						ineligible - Severe COPD		
128	255-3309	F	2*	11-01-93	03-18-94	03-22-94	OP		Disease
129	255-3310	G	2	11-22-93	03-07-94	03-09-94	OP		Disease
130	256-3221	G	4	12-02-92	---	02-22-93	increase in Pain, no objective evidence of disease progression		Disease
131	256-3222	F	4	03-24-93	04-16-93	04-20-93	OP		Disease
132	256-3223	F	2	12-16-92	---	01-15-93	investigator perception of progression, CT stable		Disease
133	256-3224	F	4	02-24-93	04-19-93	04-21-93	OP		Disease
134	256-3225	F	4	04-13-93	---	05-11-93	investigator perception of progression, CT stable		Disease
135	256-3226	G	4	11-02-93	03-11-94*	06-08-94	OP		Disease
136	256-3227	F	4	11-10-93	12-04-93	12-08-93	OP		Disease
137	256-3228	G	4	12-15-93	01-12-94	01-12-94	OP		Disease
	256-3229	F	4	12-15-93	01-07-94	01-12-94	OP		Disease
	256-3230	G	2	01-28-94	04-19-94	04-29-94	OP		Disease
140	257-3241	F	4	12-16-93	01-11-94	01-20-94	OP		Disease
141	257-3245						ineligible - No Path.		
142	258-3251	G	2	01-10-94	03-04-94	03-07-94	OP		Disease
143	258-3252						ineligible - Abnormal LFTs		Disease
144	258-3253	F	4	02-07-94	02-14-94	02-17-94	OP		Disease
145	258-3254	G	2*	02-14-94		03-28-94	Patient Refusal: Severe nausea and vomiting		
146	271-3296	G	4	10-28-93	11-12-93	12-02-93	OP		Disease
147	271-3297	G	4	01-10-94	02-03-94	03-07-94	OP		Disease
148	271-3298	F	4	01-14-94	02-07-94*	02-14-94	OP		Disease
149	271-3299	G	4	03-14-94	---	03-20-94	Death: Coagulopathy with art. and venous occlusions on coumadin after one dose of drug		Disease
150	250-3051	G	4	11-26-93	12-16-93	12-16-93	OP		Disease

Appendix: JHAY

Table 2: JHAY-Patient Response Data

No.	Study Number	Rx.	Stage	Date of Randomization	Date of Progression	Date Of Study	Response	Comments
1	201-3301	G	4*	12-21-93	02-17-94	02-17-94	SD	
2	206-3001	F	4*	09-10-92	10-05-92	10-05-92	PD	
3	206-3002						---	
4	206-3003	F	3	01-19-93	11-02-93*	02-28-94	SD	Primary increase > 25%
5	206-3004	F	4	01-28-93	04-21-93*	05-19-93	SD	New peritoneal disease
6	206-3005	G	2	02-04-93	03-02-93	03-18-93	PD	
7	206-3006						---	
8	206-3007						---	
9	206-3008	F	4	04-01-93	04-28-93	04-28-93	PD	
10	206-3009	F	3	04-15-93	05-13-93	05-13-93	PD	
11	206-3010	F	4	07-01-93	10-21-93	10-28-93	PD	CT progression
12	206-3011	G	4	11-22-93	12-27-93	12-27-93	PD	
13	206-3012	G	4	03-08-94		05-17-94.	SD	
14	210-3081	G	2*	08-26-92	01-06-93	01-13-93	SD	Consecutive CT measures not confirmatory
15	210-3082	G	4	09-30-92	01-27-93*	02-03-93	SD	CT measurements not confirmatory
16	210-3083	F	4	10-26-92	10-28-92*	11-18-92	PD	New ascites
17	210-3084	F	4	11-23-92	12-18-92	12-18-92	PD	---
18	210-3085	G	4	08-02-93	---	08-04-93	NE	
19	210-3086	F	4	09-23-93	10-19-93	10-21-93	PD	
20	210-3087	F	4	01-18-94	02-11-94	02-11-94	PD	
21	210-3088	F	2*	02-07-94	---	06-24-94	SD	
22	213-3141	G	4	01-29-93	03-22-93	03-23-93	PD	
23	213-3142	G	2*	06-01-93	---	11-22-93	SD	
24	213-3143	F	2*	06-15-93	---	09-28-93	SD	
25	213-3147	F	4	10-29-92	11-18-92	11-16-92	PD	

*Asterisk indicates disagreement between reviewer and sponsor in this area.

Appendix: JHAY

Table II: JHAY - Tumor Response Data

No.	Study Number	Drug	Stage	Date of Randomization	Date of Progression	Date Off-Study	Response	Comments
26	219-3181	F	4	09-15-92	10-27-92*	11-18-92	PD	New Ascites
27	219-3183	F	4	09-30-92	—	10-22-92	NE	
28	219-3189	G	3*	11-13-92	01-11-93	01-14-93	SD	
29	219-3185		4				—	
30	219-3187	F	4	10-16-92	11-10-92*	11-13-92	PD	New ascites
31	219-3188	F	4	11-04-92	11-30-92*	12-09-92	PD	New lung met
32	219-3190	G	4	11-17-92	01-12-93	01-20-93	PD	
33	219-3191						—	
34	219-3192	G	4	12-09-92	—	06-03-93	SD	
35	219-3193	G	3*	02-16-93	05-04-93	05-06-93	SD	
36	219-3194	G	4	02-16-93	03-08-93	03-08-93	PD	
37	219-3195	G	4	02-18-93	03-18-93*	04-12-93	PD	New liver mets
38	219-3196	F	4	02-23-93	03-23-93*	04-12-93	PD	New ascites
39	219-3197	G	4	04-05-93	04-27-93*	06-03-93	PD	New ascites; increased abd. disease
40	219-3198	G	4	04-28-93	06-30-93	07-08-93	PD	
41	219-3199	F	3	07-26-93	11-15-93*	01-10-94	SD	New liver mets
42	219-3200	F	4	08-09-93	08-30-93*	09-29-93	PD	Increase primary, liver mets
43	219-3286	G	4	08-17-93	10-20-93	11-18-93	SD	Increase primary, liver mets
44	219-3287	G	4	09-14-93	11-09-93	11-18-93	PD	
45	219-3288	G	4	10-12-93	11-10-93	11-11-93	PD	
46	219-3289	F	4	01-12-94	01-17-94	02-02-94	PD	
47	219-3290	G	4	01-14-94	—	02-21-94	NE	
48	219-3321	F	2*	01-24-94	03-28-94	04-12-94	PD	
49	219-3322	F	4	03-22-94	04-19-94	04-19-94	PD	
50	242-3281	G	4	01-19-94	03-15-94	03-15-94	PD	

Appendix: JHAY

Table II: JHAY - Tumor Response Data

No.	Study Number	Rx	Stage	Date of Randomization	Date of Progression	Date Off-Study	Response	Comments
51	249-3121	F	4	11-19-92	01-14-93	01-14-93	PD	
52	249-3122		4				—	
53	249-3123	G	2	01-19-93	03-16-93	03-17-93	PD	
54	249-3124	G	4	02-24-93	04-20-93	04-20-93	PD	
55	249-3126	F	2*	04-08-93	06-08-93*	08-22-93	PD	New ascites
56	249-3127	G	4	06-01-93	07-20-93*	08-27-93	PD	Increase in primary
57	249-3128	F	2	10-12-93	11-04-93	11-08-93	PD	
58	249-3129	F	4	11-08-93	01-04-94	01-04-94	PD	
59	249-3130	G	2*	11-15-93	—	03-21-94	SD	Alive 9-20-94
60	249-3327	G	4	01-31-94	—	—	SD	On study with stable disease
61	250-3041	F	4	10-08-92	—	11-05-92	SD	
62	250-3042	G	4	11-12-92	—	12-09-92	SD	
63	250-3043	G	4	12-21-92	06-11-93	06-17-93	SD	
64	250-3044	F	2*	12-29-92	01-14-93	01-19-93	PD	
65	250-3045	F	4	01-07-93	01-27-93	06-21-93	PD	
66	250-3046	F	4	01-18-93	02-10-93	02-10-93	PD	
67	250-3048	G	2*	02-23-93	04-15-93	06-17-93	PD	CT documented increase
68	250-3049						—	
69	250-3050	G	4	08-05-93	—	08-19-93	NE	
70	250-3052	G	3	03-23-94	04-14-94	04-20-94	PD	
71	250-3053							
72	251-3201	F	2	10-13-92	—	12-10-93	SD	
73	251-3202							
74	251-3203	G	4	07-05-93	—	07-19-93	NE	
75	251-3209	F	2	01-10-94	—	02-14-94	SD	

Appendix: JHAY

Table II: JHAY - Tumor Response Data

No.	Study No.	Rx	Stage	Date of Randomization	Date of Progression	Date Off-Study	Response	Comments
76	251-3205		4				---	
77	251-3206	G	2*	11-15-93	12-14-93*	03-28-94	PD	New ascites
78	251-3207	F	4	11-15-93	12-13-93	12-13-93	PD	
79	252-3061	G	4	11-25-92	06-29-93	08-24-93	PR	Achieved PR status on _____ Relapse in primary on _____
80	252-3062	F	4	10-14-93	---	03-15-94	SD	
81	252-3063	F	4	11-18-93	01-12-94	01-12-94	PD	
82	253-3101	F	4	07-22-92	08-10-92	08-10-92	PD	
83	253-3102	G	4	07-22-92	11-09-92	11-13-92	SD	CT showed progression, pt. had Gi bleed due to tumor
84	253-3104	F	4	08-19-92	09-02-92	09-14-92	NE	
85	253-3105						---	
86	253-3106	G	4	09-02-92	---	09-23-92	NE	Pt. refused further treatment; Will have alternative therapy
87	253-3107						---	
88	253-3108	G	4	10-21-92	11-17-92"	12-09-92	NE	
89	254-3161							
90	254-3162	G	4	04-28-93	11-08-93	02-10-94	PR	Decrease in primary with stable liver disease / _____ No study drug after _____ due AE
91	254-3163	G	3	11-10-92	---	07-13-93	NE	Unable to determine from CRF forms due to strike outs, etc.
92	254-3164	F	2	05-20-93	---	05-19-94	CR	CR documented on / _____ continues as CR: _____
93	254-3165		4				---	
94	254-3166	F	?	05-27-93	---	06-04-93	NE	Dx. in question
95	254-3167						---	
96	254-3168	F	4	06-04-93		06-08-93	NE	
97	254-3169	F	3	07-12-93	---	09-07-93	SD	Progression documented by CT on _____
98	254-3170						---	
99	254-3171			Ineligible (8-16-93): Dx in question				
100	254-3173	G	2	09-08-93	03-18-94	03-25-94	SD	

Appendix: JHAY

Table II: JHAY - Tumor Response Data

No.	Study Number	Drug	Stage	Date of Randomization	Date of Progression	Date Off-Study	Response	Comments
101	254-3174	F	4	09-08-93	---	09-23-93	NE	
102	254-3176	G	4	10-11-93	---	03-30-94	SD	CT progression on ---
103	254-3177	F	2*	11-30-93	03-07-94*	04-25-94	SD	New umbilical and inguinal nodes
104	254-3178	G	4	12-03-93	02-21-94*	05-18-94	SD	Increase in primary --- no evaluation of hepatic disease
105	254-3179	G	4	02-09-94	---	03-20-94	NE	
106	254-3180	F	4	03-16-94	03-19-94*	03-28-94	NE	Jaundice; biliary obstruction
107	255-3021	G	4	08-17-92	---	10-14-92	SD	
108	255-3022	G	4	09-14-92	02-23-93	02-23-93	SD	-
109	255-3023	G	4	11-10-92		12-01-92	NE	
110	255-3024		4				---	
111	255-3025						---	
112	255-3026	F	4	07-15-93	08-03-93	08-12-93	PD	
113	255-3027	G	2*	08-09-93	09-29-93*	11-16-93	PD	Increase in primary
114	255-3028							
115	255-3029	F	4	09-07-93	---	10-26-93	SD	
116	255-3030	F	2*	09-20-93	10-13-93	10-15-93	PD	
117	255-3031	F	2	11-24-93	12-20-93	12-21-93	PD	
118	255-3032	F	2*	11-23-93	03-11-94	03-15-94	SD	
119	255-3033	G	2*	01-10-94	---	01-27-94	NE	
120	255-3034	F	4	01-10-94	03-02-94*	04-04-94	PD	Increase in adb. mass
121	255-3035		4					
122	255-3036	F	4	01-27-94	02-02-94*	02-22-94	PD	Ascites
123	255-3037	F	4	03-03-94	06-17-94	06-18-94	SD	
124	255-3038	G	2*	03-17-94	06-15-94	06-20-94	PD	
125	255-3306	G	4	10-12-93	---	05-17-94	SD	No documentation of progression

Appendix: JHAY

Table II: JHAY - Tumor Response Data

No.	Study Number	Rx.	Stage	Date of Randomization	Date of Progression	Date Off Study	Response	Comments
126	255-3307	F	4	10-18-93	11-08-93	11-08-93	PD	
127	255-3308						---	
128	255-3309	F	2*	11-01-93	03-18-94	03-22-94	PR	PR status on: <u> </u> Increased disease <u> </u>
129	255-3310	G	2	11-22-93	03-07-94	03-09-94	SD	
130	256-3221	G	4	12-02-92	---	02-22-93	SD	
131	256-3222	F	4	03-24-93	04-16-93	04-20-93	PD	
132	256-3223	F	2	12-16-92	---	01-15-93	SD	
133	256-3224	F	4	02-24-93	04-19-93	04-21-93	PD	
134	256-3225	F	4	04-13-93	---	05-11-93	SD	
135	256-3226	G	4	11-02-93	03-11-94*	06-08-94	SD	Increase in primary on CT
136	256-3227	F	4	11-10-93	12-04-93	12-08-93	PD	
137	256-3228	G	4	12-15-93	01-12-94	01-12-94	PD	
138	256-3229	F	4	12-15-93	01-07-94	01-12-94	PD	
139	256-3230	G	2	01-28-94	04-19-94*	04-29-94	SD	New ascites
140	257-3241	F	4	12-16-93	01-11-94*	01-20-94	PD	CT progression
141	257-3245						---	
142	258-3251	G	2	01-10-94	03-04-94	03-07-94	PD	
143	258-3252							
144	258-3253	F	4	02-07-94	02-14-94	02-17-94	PD	
145	258-3254	G	2*	02-14-94		03-28-94	SD	
146	271-3296	G	4	10-28-93	11-12-93	12-02-93	PD	
147	271-3297	G	4	01-10-94	02-03-94	03-07-94	PD	
148	271-3298	F	4	01-14-94	02-07-94*	02-14-94	PD	New lung lesion; ascites
149	271-3299	G	4	03-14-94	---	03-20-94	NE	
150	250-3051	G	4	11-26-93	12-16-93	12-16-93	PD	Increase in primary

Appendix: JHAY

Table III: Clinical Benefit Response

Study No.	Rx	Stage	Response	CBR	Time	Response	Comments
206-3003	G	3	SD	R	Wk.16-48 (35)	PI ↓ AC ↓ PS 70--	On-study: 65 weeks; Cycle 1: 4wks (3 rx.); Dosage reductions subsequent cycles due to 2-4 neutropenia, thrombocytopenia gr. 2-3; after cycle 7 able to tolerate only two doses/4 wk cycle; after cycle 8 less than 50% of dose delivered per treatment; Wt. loss 19 kgs. CBR negated Wk. 48-↓ AC, ↓ PI.
255-3027	G	4*	PD*	R	Wk.1-11 (10)	PI ↓ AC -- PS 70--	On study: 14 weeks; Cycle 1-7 wks; Dose escalations 25% subsequent cycles; No missed doses; Minimal toxicity with gr. 1 thrombocytopenia; Wt. loss 4 kgs.; Considered PD due to > 25% increase in primary.
255-3037	F	4	SD	R	Wk.1-15 (15)	PI ↓ AC ↓ PS 70--	On-study: 17 weeks; Cycle 1-3 on schedule with 100% dose; Gr. 2 diarrhea with 1 in FU dose to 750 mg/m ² (cycle 3); Wt. ↓ 2 kg (? due to new ascites)
250-3043	G	4	SD*	R	Wk.3-20* (18)	PI -- AC ↑ PS 70↑	On-study: 20 weeks (CBR data reported for 26 weeks). All treatments on schedule (no treatment delays); Dose escalation to 1500 mg/m ² tolerated well; Wt. down 2 kg despite new ascites during study
250-3048	G	4*	PD*	R	Wk.4-15 (12)	PI ↓ AC -- PS 60--	On-study: 17 weeks; Rx. day 1, next treatment day 28 due to gr. 4 nausea and vomiting; Treated day 35 and day 42 (25% ↓ dose), gr. 2 thrombocytopenia; next treatment day 70 (100% dose), day 84 (50% ↓ dose) gr. 2 plts., WBC; day 91, 98, 105 (full dose)- no myelosuppression, gr. 4 nausea and vomiting, gr. 3 diarrhea; Wt. loss- 15 kg. from baseline; Baseline wt.-59 kg.;(no weights week 1,2 of study; wt. wk 3-52 kg., wt. wk 4 -53 kgs.)
252-3061	G	4	PR	R	Wk.3-29 (27)	PI ↓ AC ↓ PS 70↑	On-study: 40 wks.; All treatments on schedule; Cycle 1 -Day 43, 50 dose ↓ 50% due to neutropenia, thrombocytopenia; gr.2 nausea, vomiting; Cycle 5 (day 87): dose ↓ 25%- no myelosuppression; Cycle 6 (day 124): dose ↓ 20%- no toxicity; Wt. loss 5 kg from baseline
210-3081	G	4*	SD	R	Wk.2-18 (19)	PI ↓ AC ↓ PS 70--	On-study: 20 wks.; All treatments on schedule; Cycle 1- 8 weeks at full dose; gr.4 nausea, vomiting; gr.3-neutropenia, gr.2 dehydration; Cycle 2 day 1, 15- ↓100% dose; no treatment day 8-gr.3 neutropenia, thrombocytopenia, gr.2 AST, ALT; gr.2 vomiting; Cycle 3,4- day 1-25% ↓, day 8,14 - 56% ↓ dose due to g.2-3 neutropenia; gr.3 asthenia, gr.1 nausea and vomiting; Wt. loss-8 kg. from baseline;

* Asterisk indicates difference between applicant and reviewer in assessment in that category.

Appendix: JHAY

Table III: Clinical Benefit Response (cont.)

Study No.	Rx.	Stage	Response	CBR	Time	Parameters	Comments
253-3102	G	4	SD	R	Wk.10-15 (6)	PI ↓ AC ↓ PS-90--	On-study-16 weeks; All treatments on schedule; Cycle 2-↓ 25%; cycle 3- 120% Minimal toxicity; Last cycle developed gr.2 ↑ bili., SGOT, SGPT, gr. 3 ↑ alk. PO ₄ ; Off study due to Gi Bleed with known tumor progression; Wt. ↓ 4 kg on study; CBR lost week 16, no data on Pfor AC
249-3130	G	4*	SD	R?	Wk. 8-13 (6)	PI -- AC ↓ PS 80 --	SD by CT when pt. refused further therapy on --- --- PI scores were stable or positive week 8-13; AC consumption was positive (50% reduction) wk.8; PS is a problem: Baseline- 70; no scores week 4,6,9,13. PS ↓ 50 wk 3,5; wk. 7-60, wk. 8, 10-80, wk 12-60, wk 11-60 so pt. did not have four consecutive wks of PS. PI ↑ to > baseline on wk. 12, 13 (but not primary component). CBR lost wk 13 due to ↑ AC x 2. Cycle 1 = 8 wks, 5 doses (100%) given day 1, 8, 15, 22, 36 (Two doses missed- pt. refusal, gr. 4 neutropenia). Cycle 2- post wk 1 dose hospitalized with severe nausea and vomiting; cycle 2, wk. 2 dose held after hospitalization; Four more treatments over next 10 week period, then off study (In 19 week period pt. had 10 Rxs.) Weight stable.
254-3162	G	4	PR	R	Wk.10-41 (32)	PI ↓ AC -- PS 70 ↓	On study 41 week. AE- Pt. developed hematuria and proteinuria in --- thrombocytopenia in --- severe anemia requiring transfusion of 8 units PRBCs bet. --- and --- was placed on Prednisone 20 mg BID to treat anemia in --- developed hypertension; Pt had no drug after --- due to toxicity; No renal function studies reported. Wt. ↓ 7 kg on study.
254-3163	G	3	NE	R	Wk.12-35 (25)	PI -- AC ↓ PS 80--	On-study: 36 weeks. Cycle 1-8 wks. Dose ↓ 25% wk. 3 (AGN-300/ul, Plt.-78,000/ul); wk. 7 ↓ plts (110, 000/ul). Cycle 2 -dose ↓ 25% week 3, ↓ plts (79,000/ul). Cycle 3 not stated until 6 wks after Cycle 2 to allow marrow recovery. Cycle 3-dose 2,3 ↓ 25%, plts. ↓ (85,000/ul; 118,000/ul). Cycle 4-dose ↓ 25% wk.2, ↓ plts., wk. 3, ↓ 25% -↓ AGN. Cycle 5, wk. 3-dose ↓ 25%, ↓ plts. Cycle 6, wk. 3-dose ↓ 25%, ↓ plts. (65,000/ul). No treatment after wk. 29 due to low plts., gr.1 granulocytopenia. Plt.-123,00/ul seven weeks after last dose. Gr. I nausea all cycles. Wt. up 12kg., no ascites.
254-3164	F	2	CR	R	Wk.38-51 (13)	PI -- AC -- PS 70↑	On-study: 51 weeks. Cycle 1-100% on Schedule; ↓ 750 mg/m ² cycle 2, d.1 toxic, missed d.8,15. Wk.9-51 7 missed doses, 6↓ doses; PI stable, no analgesia required after week 11; PS stable until wk 38 when ↓ 80-90 for 4 wks noted with wk. 37 data missing. No PS wk. 51, 52.

Appendix: JHAY

Table III: Clinical Response Benefit (cont.)

Study No.	Drug	Stage	Response	CBR	Duration	Parameters	Comments
219-3190	G	4	PD	R	Wk. 4-9 (6)	PI ↓ AC -- PS 70--	On-study-9 wks.; Off study due to progressive disease; All doses 100% given on schedule; Toxicities-fever, fatigue, mucositis, and DVT requiring hospitalizations from _____ and _____ New Ascites ← Wt. ↓ 8 kg. on study.
251-3201	F	2	SD*	R	Wk. 3-9 (7)	PI ↓ AC -- PS 70--	On-study- 9 wks.; Off-study no objective evidence of progression; All treatments on schedule, 100% dose; Gr.3 nausea, vomiting, gr.1-2 diarrhea, gr. 2 asthenia both cycles. Wt. ↓ 8 kgs. on study.
249-3327	G	4	SD	R	Wk. 8-32 (26)	PI ↓ AC ↓ PS --	On-study-32 wks.; All treatments on schedule; dose ↓ 25% cycle 2, ↓ 20% cycle 3; gr.1-3 neutropenia, gr. 2 asthenia, gr. 1-3 diarrhea. Wt. ↓ 2 kg. during study
271-3297	G	4	PD	R	Wk. 2-8 (7)	PI ↓ AC ↓ PS 70--	On-study-8 wks.; One cycle (100% dose x seven wks); New ascites noted 2-3-94, on study until 3/7/94; transfused 2 units packed RBCs (Hgb - 8.2 mg%); fever, nausea, peripheral edema, gr.2 ↑ bill., SGOT, alk. PO ₄ on study; Wt. ↓ 3 kg. on study
01-3301	G	4*	SD	R	Wk. 5-8 (6)	PI ↓ AC ↓ PS 70--	On-study-9 wks.; Cycle.1-100%, all doses on schedule; cycle 2-25% 1 day; Mild somnolence, myalgia, alopecia due to drug. Off study wk 9-SBO due to tumor. Wt. ↓ 2 kgs.
255-3306	G	4	SD	R	Wk.10-31 (22)	PI ↓ AC ↓ PS 70--	On-study-31 wks.; Off-study due to clinical progression, no documentation of progressive disease. Hemochromatosis by he.; Completed cycle 1 with full dose intensity, Hgb-12.9 gm% on study; Cycle 2, day 8 omitted due to gr. 3 neutropenia, gr. 1 anemia; Cycle 3-100% dose on schedule; Cycle 4-100% dose on schedule; vomiting gr.1, pedal edema, dyspnea. Cycle 5, day 1,8 at full doses; Day 15- gr. 3 neutropenia, gr.4- anemia (Hgb-7.8 gm%, WBC-1600/ul, AGN-672/ul); amblyopia gr.1 - gr. 3. Cycle 6-100% dose day 1 only, day 8,15 held due to gr.3 amblyopia. Cycle 7, 100% dose day 1,8- Gr.4 anemia (Hgb-6.2 gm%, gr. 3-neutropenia (AGN- gr.3 thrombocytopenia (Plt-47,000/ul), gr. 1 nausea, vomiting; fever, LE edema, mental status changes with worsening vision, diarrhea; wt: 17 kg.

Appendix: JHAY

Table IV: JHAY - Study Discontinuations Due to Adverse Events

- 206-3005 Stage II, on Gemcitabine. Known to have a bipolar disorder, stable when admitted to study. Developed severe depression requiring hospitalization after initiation of treatment. Off-study on _____ due to "depression". Review of CRF indicates 25% increase in primary lesion on _____ pt. is coded in CRF as progressive disease. AE is not drug related.
- 255-3021 Stage IV, on gemcitabine. In the first cycle of therapy pt. did not receive fifth injection due to nausea. Grade 3 elevation of SGOT and SGPT occurred. During the second cycle two doses of drug were reduced 25% due to grade 2 leukopenia and thrombocytopenia. Grade I transaminase elevations persisted with moderate nausea and vomiting. The patient refused further therapy. Adverse event is clearly drug related.
- 210-3085 Stage IV on Gemcitabine. Acute antero-inferior MI on study day 2 with pulmonary edema. Past h_e. of cardiac disease. Event not drug related.
- 213-3147 Stage IV on FU. Developed increased bilirubin and alk. PO₄ due to stint obstruction after one dose of drug. Objective progression documented on _____ two days after study removal.
- 219-3290 Stage IV on Gemcitabine. Developed Gi bleed on day 28 of study. Endoscopy did not find source of bleed. Off-study on _____ days later due to progressive disease. Adverse reaction probably due to disease.
- 250-3041 Stage IV on 5-FU. After day 8 treatment complained of flu-like syndrome. Missed day 15 injection. After day 28 injection developed gr. 3 nausea and vomiting and refused further treatment. Adverse reaction is drug related, a known side effect of FU therapy.
- 250-3042 Stage 4 on Gemcitabine. Patient had three injection of Gemcitabine. Patient developed dyspnea after each injection and required inhalation treatment. Patient developed grade II neutropenia and grade II thrombocytopenia day 15 of study. Adverse event is study drug related. Dyspnea is reported to occur in up to 10% of patients on gemcitabine, cause is unclear.
- 250-3050 Stage IV on Gemcitabine. Had two injections of drug, developed maculopapular rash after first injection. Rash worst after second injection. Patient removed from study. Adverse reaction is study drug related.

Table IV: (continued)

- 253-3102 Stage IV on Gemcitabine. Had three cycles over 16 weeks without problem. Developed dehydration, fever, and Gi bleed after completion of the third cycle. Platelet count within normal limits. Developed ascites, ↑ bilirubin, and ↑ alkaline PO₄ indicating disease progression. Adverse reaction (Gi bleed) is not study drug related.
- 254-3166 Entered as Stage IV on FU. Treated with drug once. Had endoscopy which showed lower esophageal stenosis due to adenocarcinoma. Off-study due to "second" primary. Adverse event is not drug related.
- 254-3021 Stage IV on Gemcitabine. First cycle of study drug was four weeks with fifth week omitted due to neutropenia. Second cycle commenced with a 25% dose reduction due to grade 2 neutropenia, gr. 2 leukopenia, and gr. 2 elevation of SGOT and SGPT. Persistent nausea and vomiting occurred during cycle 2. Patient opted to stop therapy. Adverse reaction is drug related. (The actual incidence of vomiting is unclear due to the use of antiemetic therapy and the nature of the underlying disease, but gemcitabine does cause mild to moderate vomiting of one-two days duration in most patients.)
- 256-3230 Stage II on gemcitabine. Pt developed ascites requiring paracentesis (4.5 L removed) while on study. Had associated elevated LFTs. Paracentesis positive for malignant cells. Adverse event is disease related.
- 258-3254 Stage II on gemcitabine. Patient developed gr. 2 leukopenia with first dose of study drug. Had dose reduction. With second dose of drug pt. developed gr. 2-3 elevation of SGOT and SGPT along with gr. 3 nausea and vomiting. Adverse event is study drug related.
- 255-3303 Stage III on gemcitabine. Patient developed respiratory failure. According to CRF pt. had pulmonary emboli with severe respiratory distress and arrhythmia from which he expired. Adverse event is probably not study drug related.
- 271-3299 Stage IV on gemcitabine. Known to have coagulopathy managed with heparin and coumadin. Hospitalized just prior to onset of study to adjust anticoagulants. Received one dose of gemcitabine. _____ days later with venous and arterial occlusions. Developed gangrene of distal lower extremities, paresthesia probably due to compartment syndromes, oliguric renal failure with decreased level of consciousness. Pt. expired _____ after administration of study drug. Adverse event may be study drug related. The patient had a hypercoagulable state. Exposure to drug may have negatively influenced tumor related hypercoagulability, may have directly increased the clotting system, or had no influence on the exacerbation of the hypercoagulable state.

Table IV (continued):

- 254-3174 Stage IV pancreatic cancer with a history of gastric ulcer due to neoplastic invasion of gastric wall. Treated with FU. On ——— had massive gastrointestinal bleeding and exsanguinated secondary to disease process despite numerous transfusions. Adverse event is not drug related.
- 219-3183 Stage IV pancreatic cancer treated with FU on day 1 and day 15 of cycle 1. Developed thrombocytopenia after the first dose, so day 8 therapy was held. Received day 15 therapy without complication. On ——— chest pain and dyspnea occurred due to multiple pulmonary emboli which resulted in respiratory failure, shock, and ——— Adverse event is disease related, not drug related.

Appendix : JHAY

Table 5: Review of Radiographic Data submitted by Eli Lilly for Complete and Partial Response:

All CTs and Ultrasounds forwarded by the applicant were reviewed by Dr. Joseph Pierro (HFD-160) to determine why a discrepancy occurred between the individual investigator assessments and the Eli Lilly sponsored independent Review Board. Dr. Pierro's assessment is as follows:

JHAY

- 254-3163: No change in the hypodense area between 1-5-93 and 6-8-94
- 254-3164: A greater than 50% decrease in tumor shrinkage (PR)
- 256-3327: By measurement provided on static films the mass appears to decrease in size from 2.5 cm to 1.2 cm. (Lack of video makes this difficult to assess with one hundred per cent accuracy as the probe could be misplaced.)
- 252-3061: Ultrasound static films show a slight decrease in size., but not a 50% decrease.
- 255-3309: The CT images were 1 cm apart instead of the 0.5 cm usually used in pancreatic imaging. No appreciate difference in scans was observed with the technique used..
- 254-3162: Very difficult to delineate the lesion. Cystic dilatation of the pancreatic head with a decrease in cystic dilatation makes the definition of the tumor and evaluation of the tumor size impossible. The overall size of the head of the pancreas did not decrease 50%.

Summary: In two patients on this study partial response was confirmed. Both of these patients (254-3164 and 256-3327) were treated with FU.

VII: REVIEW OF SUPPORTING STUDY B9E-MC-JHAZ:

Title: Gemcitabine as Palliative Therapy in Patients with Progressive Carcinoma of the Pancreas

INTRODUCTION:

This phase II trial studies the effect of gemcitabine in patients with advanced or metastatic pancreatic carcinoma previously treated with fluorouracil. Seventy-four patients were enrolled for treatment evaluation, sixty-three were eligible for treatment. The various reasons why several possible participants were ineligible is presented in Table I in the appendix. The purpose of this study is to provide major support for the pivotal trial, JHAY.

PROTOCOL SUMMARY:

The protocol for this trial is very similar in content to that of JHAY. Since the JHAY protocol was summarized extensively, only the differences between the two protocols will be described in this section.

Design:

This is a single arm, non-randomized, non-blinded study.

Patient Population:

Eligibility Criteria:

Patients may have had one and only one regimen of FU prior to entrance into this study, which could include immunomodulators. (Type of FU regimen variable.)

Patients must have documented progression of disease on FU by radiographic methods.

Definition of Evaluability:

All patients who receive one dose of study drug will be evaluable and will be analyzed for efficacy and safety.

Sample Size:

A total of 56 evaluable patients will be enrolled in this study. This sample size gives a 92% chance of detecting a clinical benefit response rate of 0.25 and a 5% chance of concluding falsely that a compound with a true clinical-benefit response rate of 0.10 is effective.

The protocol was amended on July 2, 1992 as follows: "In the case that patient eligibility might be called into question once the data are collected, up to 66 patients will be enrolled. This is done in order to provide a reasonable chance that the required 56 patients are qualified for the efficacy analysis."

Dosage and Administration:

An amendment was submitted on July 2, 1992 to change the dose modifications for hematologic and non-hematologic toxicities.

Supporting Efficacy Measures:

Survival, time to progression, and duration of clinical benefit response will be defined from the first day of treatment.

Data Analysis Method:

All patients who receive the study drug will be analyzed for efficacy and safety.

The final analysis will take place six months after the last patient has been enrolled.

Analysis will include calculation of:

Clinical-Benefit Response Rate as defined by:

$$\frac{\text{No. of Clinical Benefit Responders}}{\text{No. of Patients receiving Gemcitabine}}$$

Set P_G = True clinical-benefit response rate on gemcitabine

The null and alternative hypotheses are:

$$H_0: P_G = 0.10$$

$$H_A: P_G > 0.10$$

The size of an exact binomial one-sided with 56 patients is 0.05. This test contains 92% power to detect a true response rate of $P_G = 0.25$. In addition, an observed clinical benefit response of 14/56 will result in a two-sided 95% confidence interval of (0.14, 0.36).

STUDY RESULTS:

Study Demographics:

Sixty-three patients were eligible for treatment with gemcitabine. Demographics of this group are as follows:

Sex

Male.....31 (49.2%)
Female.....32 (50.8%)

Age

Median.....62
Range.....(33-70)

Race

African Descent.....2 (3.2)
Caucasian.....57 (90.0)
Hispanic.....4 (6.3)

Clinical Stage

Stage II.....5 (7.9)
Stage III.....4 (6.3)
Stage IV.....54 (85.7)

Prior Therapy

Prior Radiotherapy & FU.....14
Prior FU Therapy.....63
Duration: < 8 days.....4
8-14 days.....6
15-21 days.....5
21-30 days.....8
30 -56 days.....17
> 56 days.....24

The stage of disease at time of entry was included in the case report form in this study. In two cases the stage was changed based on information in the case report form and indicated by asterisk in Table I in the appendix and included in the above table.

To be eligible for this protocol progressive disease had to be radiologically demonstrated on/after FU therapy. In the CRFs, a variety of FU treatment schemes were listed. Prior 5-FU therapy is indicated by the number of days that the patient remained on some type of FU regimen - CI (continuous infusion), with daily x 4 leucovorin or interferon , weekly IV, etc. Evaluation of FU exposure revealed that twenty-two patients had less than thirty days of "exposure" to FU. The CRF does not specify the date or site of progression, but notes that patient had progressive disease. Twenty-four patients had at least 56 days of FU study time, one patient was on a FU therapy for 305 days another for 480 days. Some (not specifically identified) patients were treated on the FU arm of JHAY.

Reasons for Study Discontinuations:

The following reasons for study discontinuation/continuation are reported based on the data in the CRFs. Study cut-off date was September 8, 1994.

On Study at Cut-Off.....	1 (1.5)
Pt. Refusal.....	10 (15.8)
Death on Study.....	5 (7.9)
Clinical Progression.....	3 (4.8)
Progressive Disease.....	43 (69.8)

All deaths on study were disease related. In the three cases where clinical progression (signs and symptoms of progression as perceived by the patient or physician) was the reason for study removal, one patient (206-3523) lived for six months after study discontinuation, a second (219-3606) removed from study due to increased abdominal pain remained alive for _____ and the third (249-3571) was documented to have progressive disease — month after discontinuation from study. The ten patients who refused further gemcitabine therapy did so for the following reasons:

Unknown (Could not be determined from CRF)	3
Drug Toxicity	3
Intercurrent Diseases	2
Decreased Quality of Lif.....	2

Two patients were removed from protocol by the sponsor for "interim protocol violations- one patient lived too far to come to clinic and the second had IV morphine for three days" and are included in the "unknowns".

The number of patients on study during each four week period for the first sixteen weeks is reported to help appreciate the duration of clinical benefit in terms of number of patients remaining on study.

On study > 4 weeks.....	55
On study > 8 weeks.....	37
On study > 12 weeks.....	26
On study > 16 weeks.....	13

In this study attrition during the first four weeks is not as great as on JHAY (12.6% vs. 35%).

Response Rates

Response evaluation utilized the data reported in the Current Sites of Disease pages and from other notations within the CRF. No radiographic reports were submitted. The following table compares the sponsor and the reviewer response evaluations. In doing the review, numbers in the reviewer's non-measurable and non-evaluable disease categories were less due to evidence, even if unmeasurable, of progression at other sites. Table II in the appendix includes comments for those patients where a different

response was reported by the reviewer. The six partial responses were reviewed by the applicant's internal Oncology Review Board. The board verified two of these responses. CAT scans or ultrasounds for these six patients were reviewed by an FDA radiologist. No radiographic responses were observed among the six cases reviewed by the agency. (See Table V in the Appendix.)

Table 1: Objective Response Rates

Parameter	Applicant	Reviewer
Complete (CR)	—	—
Partial (PR)	6 (9.5%)	3 (4.8%)
Stable Disease (SD)	17 (27.0%)	23 (36.5%)
Progressive Disease (PD)	20 (31.7%)	28 (44.4%)
Nonevaluable (NE)	14 (22.2%)	9 (14.3%)
Nonmeasurable	6 (9.5%)	—

Review of CRFs revealed three partial response (two of which were confirmed by the applicant's review board). Five additional patients with stable disease were reported by the reviewer. A brief summary of the partial responder's study response is presented here.

Patient 248-3618, Stage 4, with a 59 day exposure to FU began treatment on 6-10-93. PR by tumor measurements on _____ Progression noted with development of bony met in the lumbar spine on 3-15-94. Death on _____ Not all CT were done at the same site, but all were read at the study site. Duration of partial response: 117 days.

Patient 250-3591, Stage 3, with a 30 day exposure to FU began treatment on 2-9-93. PR was noted 3-16-93. Patient refused further treatment on _____ Progression documented by CT on _____ Duration of response: 126 days

Patient 252-3541, Stage 4, with 97 day exposure to FU began treatment on 4-19-93. PR noted on _____ Progression documented on _____ Death on _____ Duration of Response: 85 days.

The objective tumor response rates (based on CRF review) is 4.8% with 95% confidence interval of 0-10%.

Time to Progression:

Time to progression in this review is defined as the time between the date of informed consent (or first day of treatment) to the day of progression. (In the protocol time to progression is defined as time from date of treatment to date of progression or time when patient is removed from study.) The median time to progression is 61 days (95% confidence intervals: 56 - 85 days) with a range of 0 - 531 days. Nine patients (14.2%) were not evaluable for response and seven patient (censoring rate: 13%) did not

progress on study.

Time to Treatment Failure

Time to treatment failure is defined at the time from the date of treatment to the date the patient is removed from study for any reason - progression, death, refusal, adverse event. Based on review of the CRFs median time to treatment failure is 57 days (95% confidence interval: 36 - 64 days) with a range from 0 - 531 days. One patient (1.6%) was censored as he was on treatment at study cut-off date.

Survival

Survival analysis measures the time interval from the date of treatment to the date of death. Median survival time on this study was 119 days (95% confidence interval: 96 - 149 days) with a range of 0-531 days. Five patients (7.9%) were censored in this analysis.

Clinical Benefit Response:

Seventeen patients were reported as clinical benefit responders in this trial. The clinical course of each of these responders is summarized in Table III in the appendix. The parameter(s) which led to the designation of clinical benefit response are listed here:

Reduction in Pain Intensity.....	5
Improved Performance Status.....	4
Decreased Analgesia Consumption.....	4
Reduction in PI, Decreased AC.....	3
Improvement in PI, AC, and PS.....	1

In twelve patients subjective (reduced pain intensity) and objective (reduced analgesia consumption, improved performance status) improvement of clinical benefit was reported. Objective tumor response (as judged from the CRFs) for the clinical benefit responders is as follows: (1) Two had objective partial tumor responses; (2) Thirteen had stable disease; and (3) Two had progressive disease.

Clinical benefit response designation was achieved for 10 patients within the first four weeks of therapy, for six patients within the second four weeks of therapy, and for one patient in the third four weeks of therapy. The duration of clinical benefit response is from 4-69+ weeks with a breakdown by eight week periods as shown in the following table:

CBR ≤ 8 weeks.....	1
CBR 9 - 16 weeks.....	9
CBR 17- 24 weeks.....	2
CBR 25- 32 weeks.....	2
CBR ≥ 33 weeks.....	3

One patient (248-3614) remained a clinical benefit responder at study-cut off (69+ weeks) and has been enjoying an active lifestyle. This patient had been on a reduced dose (75% of the starting dose) since cycle 6 due to myelosuppression but has had no other toxicities. Another patient (248-3618) also a PR had minimal toxicity with full schedule of therapy (no dose escalations). Two patients died on study as clinical benefit responders, one _____ due to a GI bleed and one _____ from disease. One patient (250-3591) refused further treatment as a clinical benefit responder possibly related to drug toxicities. One patient _____ had increased abdominal pain which resulted in a morphine overdose (suicide attempt per CRF) and, after increased analgesia could not control pain, was removed from study and referred for RT.

In looking at centers at which the clinical benefit responders were treated, one responder was reported from each of three centers (enrollment per center: 2, 5, 4), three responders were reported from each of two centers (enrollment per center: 9,9), and nine responders were reported from one center (enrollment per center: 16).

SAFETY ANALYSIS

Deaths on Study:

Five deaths were reported on this study. All were disease related.

Hospitalizations:

Twenty-four patients were hospitalized on thirty-two occasions while on study. (Two additional patients were hospitalized for pain stabilization prior to therapy.) Of these hospitalizations twenty were directly related to the underlying disease process or complications due to the disease, in seven drug therapy with possible exacerbation of disease was the reason, and in five hospitalization was related to other health problems/surgical procedures. The hospitalizations considered to be related to therapy (or therapy related exacerbations of symptoms of underlying disease) included seven for nausea and vomiting \pm dehydration, two for febrile reactions, one for lower extremity edema, one for flu-like symptoms and one for fatigue with anemia. In this study six patients (9.6%) developed disease related deep venous thrombosis requiring hospitalization.

Study Discontinuations due to Adverse Events:

Seven patients were discontinued from study due to adverse events (including the five deaths noted above). A summary of the clinical course of these patients is included in Table III in the appendix. In the CRF review ten patients were identified as study discontinuations due to treatment refusal. One case considered a discontinuation due to an adverse event by the sponsor (patient 219-3606 discontinued due to severe abdominal pain) was judged by the reviewer to have clinical progression as a reason for removal from study.

Nine patients refused therapy, but none were considered to have had an adverse events. Of these nine, two (256-3631, 256-3632) refused therapy due to a "decrease in quality of life" without specifically citing

any other reason, four refused for reasons related to study drug toxicity, two refused due to other adverse events related to the underlying disease process, and one patient refused in order to seek alternative therapy. The cases which are not included in Table IV (Discontinuations for Adverse Events) in the appendix are discussed here:

Patient No.	Summary
213-3582	Stage IV. Therapy initiated on 10-5-93. Patient had three doses of Cycle 1 when fever, chills, nausea, and vomiting, Rt. pleural effusion developed. Patient was found to have multiple liver abscess and was treated with antibiotics. The patient refused therapy and was taken of study on _____. Patient died from progressive disease on _____.
219-3602	Stage IV. Therapy initiated on 9-14-92. Had one dose only. Developed gr. 4 dyspnea, gr. 4 nausea and vomiting, dehydration, backache, and required hospitalization on _____ due to the severity of symptoms. Hgb _____ was 11.0 gm%, had dropped to 8.7 gm% so pt. was transfused two units of packed cells. Patient appeared to develop an ileus (?SBO). On _____ the patient developed recurrent DVT. On _____ bilateral pleural effusions were noted. Patient removed from study on _____ for "progressive disease and toxicity" No toxicity grading > 0 is reported on the WHO Toxicity Grading form (in the CRF) for this visit.
219-3607	Stage IV. Therapy initiated on 7-13-93. Had one injection only. One week after initial injection patient developed a stint blockage, followed by cholangitis when the stint was changed. Patient experienced thrombocytopenia (plts. ↓ 80,000/ul 7/21), fever due to drug injection, rash, mucositis, with drug. On _____ patient refused further therapy citing problems such as rectal pain and dysuria. Patient expired _____.
219-3608	Stage IV (?III). Therapy initiated on 8-25-93 with a 25% dose reduction weeks 4-7 due to gr. 3 granulocytopenia. Patient had gr. 2 nausea and vomiting, gr. 2 mucositis, gr. 1 diarrhea. At the time patient refused further therapy she had evidence on CT scan of progression. Patient died/_____.
219-3609	Stage IV. Therapy initiated on 10-18-93. Patient received first cycle on schedule with dose reductions weeks 5-7 due to gr. 2-3 neutropenia. Patient experienced fever and fatigue, gr. 2 nausea and vomiting and discontinued treatment on _____. Reason given for discontinuation in the CRF, "Better quality of life off drug". Patient expired on _____.
256-3631	Stage IV. Therapy initiated on 11-4-92. Cycle I was seven weeks with dose reduced 50% weeks 5 and 6 due to gr. 2 neutropenia. Pt. had gr. 3 nausea and vomiting, gr. 2 diarrhea, and fatigue throughout cycle and refused further therapy on _____. Patient expired _____ from disease.
256-3632	Stage IV. Therapy initiated on 5-4-93. Patient had one dose with fatigue, gr. 1 nausea and

vomiting, gr. 1 anorexia, gr. 1 diarrhea, and edema. She refused further on 5-12-93 stating that she "feels better off chemo". Patient expired on _____

271-3681 Stage IV. Therapy initiated on 2-11-94. After one dose patient decided to seek alternative therapy _____ reported to have a 99% chance of cure in this disease. The patient expired from disease on _____

250-3591 Stage IV. This patient is a clinical benefit responder who was on study for 19 weeks. He refused further therapy even with documented partial response. Patient had problems with gr. 2-3 nausea and vomiting and grade 3 asthenia even with dose reductions. Progression on CT scan was noted one week after patient removed from study.

Summary of Doses Given During Weeks 1 - 8:

The length of the first cycle ranged from 4 - 9 weeks. The following table is included to provide information on the number of patients able to complete a full (seven weeks of treatment with a one week rest) first cycle of therapy, how many of these patients were able to continue therapy in cycle 2 (4 weeks), and how many patients, unable to completed a full first cycle of therapy (< seven weeks), were able to continue treatment in cycle 2.

Table 2: Injections during Cycle 1

No. of Injections during Cycle 1	No. of Patients	No. of Patients Continuing to Cycle 2
1	7	2
2	1	1
3	9	4
4	13	6
5	6	3
6	10	5
7	17	14

Seventeen of sixty-three (27%) patients completed the prescribed seven injections for cycle one. Thirteen per cent of all patients had one dose reduction during cycle one. About half of the patients who received less than seven injections in cycle one continued on to cycle two. Disease progression, death, or patient refusal account for those patients (54%) who did not continue on to cycle 2.

Dose Escalations, Reductions, and Omissions:

The following list presents information about the dose intensity of the injections given on trial.

No. of Protocol Defined Injections.....	656 (100.0%)
Actual Injections Administered.....	582 (88.8%)
Given as Assigned.....	369 (56.3%)
Escalated.....	69 (10.5%)
Reduced.....	144 (22.0%)
Omitted.....	74 (11.3%)

In the first cycle (4-9 weeks) 297 injections were given of which 13.9% were reduced and 12.1% were omitted. In the second cycle (4 weeks) 35 patients remained on study and 92 injections were given (2.3 injections / patient). Dose reductions occurred in 24.5%, dose omissions in 6.1%, while escalations occurred in 19.4% of the doses administered during the second cycle. In the third cycle 22 patients remained on study and 55 injections were given (2.5 injections per patient). Dose reductions occurred in 22.2%, omissions in 12.7%, and escalations in 19%. In the fourth cycle 13 patients remained on study. A significant number of patients could not tolerate the dose schedule/intensity of this trial due to their overall condition and the toxicities of the study drug.

Reasons for the dose omissions are as follows: (1) leukopenia 15.8%, (2) thrombocytopenia 10.5%, (3) "comment" 48.7%, (4) unspecified 8.7%. In the "comment" section the most frequent reasons given for dose reduction are neutropenia, thrombocytopenia, nausea, and concurrent hospitalization. In "unspecified" , the reasons include the investigator's judgement not to escalate dose due to overall condition of patient or due to drug toxicity in the previous cycle.

Dose reductions occurred for the following reasons: (1) leukopenia - 21.4%, (2) thrombocytopenia- 19.4%, (3) anemia - 1.0%, (4) unspecified - 13%, and (5) comments - 35%. In the "comments" group reasons such as neutropenia, thrombocytopenia, nausea and vomiting were listed most often. In the unspecified group, reasons listed included investigator decision based on toxicity events of previous cycle or the patient's overall condition.

Treatment Emergent Signs and Symptoms:

Data was collected on any signs or symptoms which a patient manifested at least once during treatment. The signs and symptoms which could be judged to be the result of therapy (realizing that sometimes the disease causes the same symptoms) are presented in the following table. Signs and symptoms (ie. ascites, pleural effusion, and pain) related to the underlying disease process are omitted from the table.

In Table 3 the most frequent treatment related signs and symptoms, which were considered drug-related, are nausea (65%), vomiting (54%), asthenia (53.2%), anorexia (39.7%), diarrhea (38.1%), and leukopenia (33.3%). These symptoms were graded and reported in the WHO grade toxicity grading in the following section.

Table 3: Treatment Emergent Signs and Symptoms

TESS	No. with Sign/Symptom	No. at Risk	Per Cent (%)
Asthenia	33	62	53.2
Flu Syndrome	10	63	15.9
Headache	4	63	16.5
Malaise	4	63	6.3
Chills	16	63	25.4
Fever	27	63	42.9
Fever with Leukopenia and Infection	5 2		
Infections	6	63	9.5
Cellulitis	2		
Pneumonia	1		
Hepatic Abscess	2		
Sepsis (Stint Infection)	1		
Mucositis	1	63	1.6
Injection Site Reactions	3	63	4.8
Dehydration	5	63	7.1
Edema	8	63	12.7
Generalized Edema	2	63	3.2
Peripheral Edema	14	63	22.2
Dyspnea	9*	63	14.3
Cough Increased	2	63	9.5
Pleural Effusion	5	63	7.9
Alopecia	9	63	14.3
Rash	11	63	17.5
Amblyopia	2	63	3.2
Taste Perversion	2	63	3.2
Nausea	41	63	65.1
Vomiting	34	63	54.0
Anorexia	25	63	39.7
Diarrhea	24	63	38.1
Anemia	10	63	15.9
Leukopenia	21	63	33.3
Pancytopenia	1	63	1.6
Thrombocytopenia	18	63	28.6

*Three patients with dyspnea had pulmonary metastases.

WHO Toxicity Grading Profile:

The following tables present the overall toxicity grading for any toxicity which may have occurred once or more than once for a particular patient during any cycle.

Hematologic Toxicity:

Hematologic toxicity was mild in these previously treated patients with less than 20% of the patients experiencing greater than grade II myelosuppression. One patient developed gr. 3 anemia with gr. 3 thrombocytopenia due to drug induced myelosuppression with normal creatinine levels. No cases of hemolytic anemia were identified. In order to better appreciate the myelotoxicity profile the worst WHO grade for patients at risk for cycles 1 - 4 with reference to the baseline values is presented in Table

5

Table 4: Hematologic Toxicity Grading

Parameter	No. of Patients (Total No. = 61)	Per Cent (%)
Hemoglobin		
Gr. I (9.5 -10.0 g/100ml)	20	32.8
Gr. II (8.0 -9.4 ")	23	37.7
Gr. III (6.5 -7.9 ")	6	9.8
Gr. IV (<6.5 ")	1	1.6
No. of RBC Transfusions	11	
WBC Counts		
Gr. I, II		59.0
Gr. III		9.8
Gr. IV		0.0
Neutrophil		
Gr. I (1.5 -1.9/mm ³)	14	23.0
Gr. II (1.0 -1.4/ ")	7	11.5
Gr. III (0.5 -0.9/ ")	15	15.0
Gr. IV (<5.0/ ")	1	1.0
Platelets		
Gr. I (75 -99/mm ³)	16	26.2
Gr. II (50 -74/ ")	7	11.5
Gr. III (25 -49/ ")	3	4.9
Gr. IV (<25/ ")	-	-

Table 5: Hematologic Toxicity by Cycle (1-4)

Parameter	Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
(No. of Patients/ Cycle)	63	63	34	23	13
Hemoglobin Gr. 0	48	14	13	9	7
Gr. I	12	24	14	7	3
Gr. II	3	18	5	7	3
Gr. III	0	4	0	0	0
Gr. IV	0	1	0	0	0
WBC Gr. 0	62	22	16	10	6
Gr. I	1	18	6	7	3
Gr. II	0	16	9	3	0
Gr. III	0	5	0	3	0
Gr. IV	0	0	0	0	0
Neutrophils Gr. 0	61	26	18	9	8
Gr. I	0	17	5	3	0
Gr. II	0	6	3	3	1
Gr. III	0	12	5	6	4
Gr. IV	1	0	0	1	0
Platelets Gr. 0	63	44	25	18	9
Gr. I	0	14	6	3	2
Gr. II	0	2	3	2	2
Gr. III	0	1	0	0	0
Gr. IV	0	0	0	0	0

Myelotoxicity does not appear to be cumulative based on the small number of patients who have prolonged exposure to the drug. Transfusion of red blood cells was reported for eleven patients.

Hepatic Toxicity

Hepatic toxicity is difficult to grade as the majority of the patients in this study had liver metastases on entry. Alkaline phosphatase abnormalities are not reported for this reason. The following table summarizes the changes in ALT and AST for the first four cycles of therapy as compared to baseline grade.

Table 6: Hepatic Toxicity Grading by Cycle (Cycles 1-4)

Parameter	Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
No. of Patients/Cycle	63	63	34	23	13
ALT Gr. 0	50	22	17	13	6
Gr. I	11	25	13	4	4
Gr. II	0	8	3	3	3
Gr. III	2	5	0	1	0
Gr. IV	0	0	0	0	0
AST Gr. 0	49	19	13	7	5
Gr. I	10	23	16	10	6
Gr. II	3	12	4	3	2
Gr. III	1	4	0	1	0
Gr. IV	0	2	0	0	0

Drug related increases in ALT and AST appears in the first few cycles and are usually gr. 1-2 and generally resolve even with continued exposure to the drug.

Renal Toxicity

Three patients (4.8%) developed proteinuria and hematuria. Grade I creatinine elevation (1.26 - 2.5x normal) was reported in four patients. In one patient the hematuria can be attributed to renal calculi. No cases of hemolytic-uremic syndrome were reported and no cases of sustained renal dysfunction were reported.

Gastrointestinal Toxicities:

Nausea with vomiting of Gr. I/II level was reported in 32 (50.8%) patients while 4 patients experienced gr. 3 and one patient experienced gr. 4 vomiting. The following table presents the level of toxicity for the first four cycles. No baseline information is available so interpretation should be made with the thought that some patients had nausea and vomiting of varying degrees and were on antiemetic therapy at entry into the study.

Table 7: Nausea and Vomiting by Cycle (Cycles 1-4)

Parameter	Cycle 1	Cycle 2	Cycle 3	Cycle 4
No. of Patients/Cycle	63	34	23	13
Nausea and Vomiting				
Grade 0	32	20	23	9
Grade I	13	6	12	2
Grade II	14	7	4	1
Grade III	4	1	5	0
Grade IV	0	0	1	1

In about half of the patients treated with gemcitabine nausea and vomiting occurred despite antiemetic therapy and in few patients nausea and vomiting were severe.

Diarrhea usually related to drug therapy occurred in twenty patients. In sixteen patient the severity was grade I, in three the severity was grade 2. One patient developed grade 3 diarrhea due to C. difficile enterocolitis which resulted resulting in hospitalization in cycle 1.

Grade I mucositis was reported in nine patients and the tenth patient had grade II mucositis (but appears to have an underlying herpetic infection which flared on treatment).

Other Toxicities

Other toxicities reported with grading in this study include:

Allergic reaction gr. I.....2/61 (3.2%)

Cutaneous Toxicity, gr. I-II.....	6/57 (9.5%)
Alopecia, gr. I-II.....	10/57 (15.9%)
Neurotoxicity gr. I-II.....	2/63 (3.2%)
Fever	20/63 (31.7%)
Gr. 3, with pneumonia.....	1
Gr. 2.....	9
Gr. 1.....	7

SUMMARY:

Sixty-three patients, with previous exposure to FU, were treated with gemcitabine. Fifty-five patients were on study for more than four weeks and thirty-seven patients for greater than 8 weeks. Three partial responses were observed based on information within the case report forms for a response rate of 4.8% (95% confidence interval: 0 - 10%). Median time to progression was 61 days (95% confidence interval: 56-85 days) with a range of 0 - 531 days. Median time to treatment failure was 57 days (95% confidence interval: 36 -64 days) with a range from 0 - 531 days. Median survival time was 119 days (95% confidence interval: 96 - 149 days) with a range of 0 -531 days. Seventeen clinical benefit responses (27%) were observed with a duration from 4 - 69+ weeks.

No deaths were related to study drug therapy. Nine patients discontinued study due totally or in part to study drug toxicity. The major toxicities of gemcitabine as reported in this study: nausea - 65%, vomiting - 54%, asthenia - 53%, anorexia - 39.7%, diarrhea - 38.1%, fever (without infection or neutropenia) - 31.7%, chills - 25.4%, edema 12 - 37%, and flu-like syndrome - 15.9%. Myelosuppression including anemia, neutropenia, and thrombocytopenia of grade 3-4 is seen in less than 20% of patients. Dose reduction and dose omissions occurred in about one third of the patients. With regard to cumulative toxicity none was noted, but only nine patients entered the fifth cycle of therapy.

Appendix JHAZ

Table 1: JHAZ - Patient Data

No.	Study No.	Stage	FU exposure (days)	Date of Treatment	Date of Progression	Date of Death	Response	Comments
1	206-3521					—		Pt. refused to be on study —
2	206-3522	4	62	11-20-92	01-14-93	—	PD	Died from disease
3	206-3523	4	28	05-05-93	06-02-93	—	NE	No change on CT, clinical decline; died from disease
4	206-3524	4	7			—		Ineligible — bilirubin high; died of disease
5	206-3525	3	21	06-03-93	07-01-91	—	PD	New bone mets and node; died from disease
6	206-3526	4	112	06-03-93	06-10-93	—	NE	Stint obstruction and SBO/ileus — died from disease
7	206-3527	4	38	09-09-93	10-21-93	—	PD	Developed gastric outlet obstruction — died from disease
8	210-3551	4	42	09-02-92	10-28-92	—	PD	Increase in pulmonary mets; died from disease
9	210-3552	4	132	10-19-92	11-16-92	—	PD	New brain met.; died of disease
10	210-2553	4	14	12-28-92	—	—	NE	Pt. refused further therapy — due to toxicity- gr.4 nausea, vomiting, asthenia, gr.2 somnolence; died of disease
11	210-3554	4	14	—		—		Ineligible — Bilirubin increased
12	210-3556	4	20	03-01-94	04-07-94	—	PD	Died of disease
13	210-3581	4	192	03-16-93	06-02-93	—	SD	New ascites, pleural effusion — Died of disease
14	213-3582	4	74	10-05-93	—	—	NE	Off-study — due to patient refusal after treatment of hepatic abscesses required hospitalization from — to — no therapy after —
15	219-3601	4	41	08-13-92	10-08-92	—	PD	New liver met; Alive —

Table I: JHAZ - Patient Data Base

No.	Study No.	Stage	FU Exposure (Days)	Date on Treatment	Date of Progression	Date of Death	Response	Comments
16	219-3602	4	32	09-14-92	09-24-92	—	NE	Off-study 09-24-92 due AE: Severe nausea, vomiting with dehydration, dyspnea, peripheral edema, bilateral pleural effusion, anemia requiring 2 units RBIS: developed DVT
17	219-3603	4	56	12-03-92	01-07-93	—	PD	Progressive disease on CT died of disease
18	219-3604	4	88	01-15-93	04-30-93	—	SD	Progression in liver; Off study on died from disease
19	219-3605	4	42	04-27-93	05-17-93	—	PD	Increase in primary with new ascites on Off-study on died of disease
20	219-3606	4	88	06-10-93	—	—	SD	Off-study 10-14-93 due to increased abdominal pain; died of disease
21	219-3607	4	52	07-13-93	—	—	NE	Off-study 08-05-93: Pt. refused further therapy because of other physical problems
22	219-3608	3	162	08-25-93	—	—	SD	Off-study 10-21-93: Pt refused further therapy due to study drug toxicity
23	219-3609	4	43	10-18-93	—	—	SD	Off-study 12-13-93: Pt. refused further therapy due to study drug toxicity
24	219-3611	4	34	01-04-93	04-06-93	—	SD	DOS: GI bleed; Pt placed on Motrin CT showed increase in pancreatic mass
25	248-3612	4	140	01-20-93	05-05-93	—	SD	Died of disease
26	248-3613	4	37	02-19-93	05-12-93	—	SD	New ascites died of disease
27	248-3614	4	89	03-18-93	—	—	SD	(Alive on study)
28	248-3615	4	167	03-24-93	04-14-93	—	PD	Off-study (5-18-93): Pt. refused further therapy; CT shows 37% increase in primary on with liver mets stable
29	248-3616	4	32	04-27-93	—	—	NE	DOS: New ascites Had I&D of hepatic abscess due to clostridia on had PTE on died with hepatic failure, ? etiology
30	248-3618	4	59	06-10-93	03-15-94	—	PR	PR Developed bony met to lumbar spine on died of disease

Appendix: JHAZ

Table 1: JHAZ - Patient Data Base

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Date of Death	Response	Comments
50	250-3591	3	30	02-09-93	---	---	PR	PR --- patient refused further treatment on --- Progression documented on --- with hepatic met; died from disease
51	251-3621	4	60					Ineligible / --- due elevated LFTs; died from disease
52	251-3623	4	32	09-22-93	10-20-93	---	PD	New ascites --- died from disease
53	251-3625	4	21	01-06-94	03-10-94	---	PD	Increase in hepatic disease; died from disease
54	252-3541	4	97	04-19-93	11-24-93	---	PR	PR --- with progression on --- died from disease
55	252-3542	4	45	01-28-94	02-03-94	---	PD	Developed ascites --- ; died from disease
56	252-3543	4	119	03-08-94	04-04-94	---	PD	Increase in all disease sites; Died from disease
57	253-3561	4	30	08-26-92	09-30-92	---	PD	Died from disease
58	253-3562	4	28	12-08-92	03-23-93	---	SD	Progressive disease in pancreas; died from disease
59	253-3563	4	28	05-05-93	05-20-93	---	PD	New ascites; Died from disease
60	253-3564	3	91	07-21-93	09-13-93	---	PD	Hospitalized with SBO due to progressive disease --- died from disease
61	253-3565							Ineligible: No histological Dx.; elevated LFTs
62	254-3591							(Incomplete CRF)
63	254-3592	4	150	03-30-93	05-25-93	---	PD	New lung lesion; Pt. lost to F/U
64	254-3593	2*	60	04-13-94	07-20-93	---	SD	Increase in primary, no evidence of nodes or mets in CRF; died from disease
65	254-3594	2*	305	08-16-93	11-04-93	---	PD	Initial CT indicated 3 x 2 cm lesion; On --- 4 x 4 cm.; confirmed on --- . Pt. on study until --- when jaundice developed; died from disease
66	254-3595	4	49	09-22-93	10-22-93	---	PD	New ascites on --- with increase in primary; died from disease
67	256-3631	4	14	11-04-92	---	---	SD	Pt. refused further therapy on --- because "quality of life was decreasing due to side effects"; died from disease

Table I: JHAZ - Patient Data Base

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Date of Death	Response	Comments
31	248-3619	4	325	06-23-93	10-28-93	—	SD	New hepatic met — died from disease
32	248-3620	4	42	09-01-93	11-24-93	—	SD	New hepatic mets; died from disease
33	248-3675	4	30	09-01-93	05-04-94	—	SD	Marked variability in the CT measurements from month to month with increase in size in — Off study 6-24-94 because of new lung met on —
34	248-3676	4	40	11-08-93	12-06-93	—	PD	Increase in hepatic mets; died from disease
35	248-3677	4	13	11-22-93	01-21-94	—	SD	Increase in hepatic mets; died from disease
36	248-3678	4	194	11-18-93	02-23-94	—	SD	DOS: disease
37	248-3679	2	480	11-30-93	08-02-94	—	SD	Received Procrit in — for anemia
38	248-3680	4	72	01-26-94	02-22-94	—	PD	DOS: New ascites — Died from GI bleed on —, probably related to disease
39	249-3571	4	48	01-27-93	—	—	SD	Off-study on 04-21-93 due to "lack of efficacy" with stable disease on CT scan; Progressive disease documented on — died from disease
40	249-3572	2	19	11-15-93	12-04-93	—	PD	DOS: disease
41	249-3573	4	52	02-01-94	04-20-94	—	PD	Progression of liver mets; died from disease
42	250-3531	4	60	10-13-92	11-03-92	—	PD	New ascites on — with new peritoneal implant —, off-study on: —
43	250-3532	2	7	02-09-93	04-30-93	—	SD	New lymph node; died from disease
44	250-3533	4	22	02-09-93	03-02-93	—	PD	Increase in liver mets; Died from disease
45	250-3534	4	59	02-10-93	04-07-93	—	PD	Increase in primary and liver mets; died from disease
46	250-3535	4	14	02-10-93	04-08-93	—	PD	New subcutaneous abdominal mass and increase intraabdominal disease; died from disease
47	250-3536		7			—		Ineligible: Pain not stabilized
48	250-3537	4	16	02-24-93	06-03-93	—	SD	New liver met; Died from disease
49	250-3538	4				—		Ineligible: Severe COPD

Appendix: JHAZ

Table 1: JHAZ - Patient Data Base

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Date of Death	Response	Comments
68	256-3632	4	27	05-04-93	---	---	NE	Pt. refused further therapy on . --- "feels better off chemo"; Died from disease
69	256-3633	4	25	06-08-93	09-27-93	---	SD	Progressed in liver, Died from disease
70	256-3635	4	20	12-22-93	01-19-94	---	PD	Progression of primary and in lung; died from disease
71	271-3681	4	7	02-11-94	---	---	NE	Pt. refused therapy on . --- , died from disease

Table II: JHAZ - Patient Treatment Evaluation

No.	Study No.	Stage	FU exposure (days)	Date of Treatment	Date of Progression	Response	Date Off-Study	Comments
1	206-3521							Pt. refused to be on study —
2	206-3522	4	62	11-20-92	01-14-93	PD	01-14-93	
3	206-3523	4	28	05-05-93	06-02-93	NE	06-02-93	No change on CT, clinical decline
4	206-3524	4	7					Ineligible — : bilirubin high
5	206-3525	3	21	06-03-93	07-01-93	PD	07-08-93	New bone mets and node
6	206-3526	4	112	06-03-93	06-10-93	NE	06-10-93	Stint obstruction and SBO/ileus —
7	206-3527	4	38	09-09-93	10-21-93	PD	10-21-93	Developed gastric outlet obstruction —
8	210-3551	4	42	09-02-92	10-28-92	PD	12-02-92	Increase in pulmonary mets
9	210-3552	4	132	10-19-92	11-16-92	PD	11-16-92	New brain met.
10	210-2553	4	14	12-28-92	—	NE	01-19-93	Pt. refused further therapy — due to toxicity- gr.4 nausea, vomiting, asthenia, gr.2 somnolence; died of disease
11	210-3554	4	14	—				Ineligible — Bilirubin increased
12	210-3556	4	20	03-01-94	04-07-94	PD	04-07-94	
13	210-3581	4	192	03-16-93	06-02-93	SD	06-10-93	New ascites, pleural effusion —
14	213-3582	4	74	10-05-93	—	NE	12-02-93	Off-study 12-2-93 due to patient refusal after treatment of hepatic abscesses required hospitalization from: — to — no therapy after —
15	219-3601	4	41	08-13-92	10-08-92	PD	10-10-92	New liver met; Cause of death unknown

Table II: JHAZ - Patient Treatment Evaluation

No.	Study No.	Stage	FU Exposure (Days)	Date on Treatment	Date of Progression	Response	Date Off-Study	Comments
16	219-3602	4	32	09-14-92	09-24-92	NE	09-24-92	Off-study 09-24-02 due AE: Severe nausea, vomiting with dehydration, dyspnea, peripheral edema, bilateral pleural effusion, anemia requiring 2 units RBIS: developed DVT
17	219-3603	4	56	12-03-92	01-07-93	PD	02-08-93	Progressive disease by CT on
18	219-3604	4	88	01-15-93	04-30-93	SD	06-03-93	Progression in liver, Off study on
19	219-3605	4	42	04-27-93	05-17-93	PD	07-13-93	Increase in primary with new ascites on Off-study on 07-13-93
20	219-3606	4	88	06-10-93	---	SD	10-14-93	Off-study 10-14-93 due to increased abdominal pain
21	219-3607	4	52	07-13-93	---	NE	08-05-93	Off-study 08-05-03: Pt. refused further therapy because of other physical problems
22	219-3608	3	162	08-25-93	---	SD	10-21-93	Off-study 10-21-93: Pt refused further therapy due to study drug toxicity
23	219-3609	4	43	10-18-93	---	SD	12-13-93	Off-study 12-13-93: Pt. refused further therapy due to study drug toxicity
24	219-3611	4	34	01-04-93	04-06-93	SD	04-09-93	DOS: from GI bleed; Pt placed on Motrin CT on showed increase in pancreatic mass
25	248-3612	4	140	01-20-93	05-05-93	SD	06-16-93	
26	248-3613	4	37	02-19-93	05-12-93	SD	06-07-93	New ascites
27	248-3614	4	89	03-18-93	---	SD		(Alive on study)
28	248-3615	4	167	03-24-93	04-14-93	PD	05-18-93	Off-study (5-18-93): Pt. refused further therapy, CT shows 37% increase in primary on with liver mets stable
29	248-3616	4	32	04-27-93	---	NE	06-15-93	DOS: New ascites Had I&D of hepatic abscess due to Clostridia on had PTE on died with hepatic failure, ? disease
30	248-3618	4	59	06-10-93	03-15-94	PR	03-15-94	PR Developed bony met to lumbar spine on died of disease

Appendix: JHAZ

Table II: JHAZ - Patient Treatment Evaluation

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Response	Date Off-Study	Comments
31	248-3619	4	325	06-23-93	10-28-93	SD	11-02-93	New hepatic met
32	248-3620	4	42	09-01-93	11-24-93	SD	11-24-93	New hepatic mets
33	248-3675	4	30	09-01-93	05-04-94	SD	06-21-94	Marked variability in the CT measurements from month to month with increase in size in Off study 6-24-94 because of new lung met on
34	248-3676	4	40	11-08-93	12-06-93	PD	12-06-93	Increase in hepatic mets
35	248-3677	4	13	11-22-93	01-21-94	SD	01-25-94	Increase in hepatic mets
36	248-3678	4	194	11-18-93	02-23-94	SD	02-23-94	DOS: disease
37	248-3679	2	480	11-30-93	08-02-94	SD	08-16-94	Received Procrit in for anemia
38	248-3680	4	72	01-26-94	02-22-94	PD	03-06-94	DOS: New ascites on Died from GI bleed, probably related to disease
39	249-3571	4	48	01-27-93		SD	04-21-93	Off-study on ; due to "lack of efficacy" with stable disease on CT scan; Progressive disease documented on
40	249-3572	2	19	11-15-93	12-04-93	PD	12-21-93	DOS: disease
41	249-3573	4	52	02-01-94	04-20-94	PD	04-20-94	Progression of liver mets
42	250-3531	4	60	10-13-92	11-03-92	PD	02-23-92	New ascites on ; with new peritoneal implant ; off-study on
43	250-3532	2	7	02-09-93	04-30-93	SD	05-10-93	New lymph node
44	250-3533	4	22	02-09-93	03-02-93	PD	03-02-93	Increase in liver mets
45	250-3534	4	59	02-10-93	04-07-93	PD	05-05-93	Increase in primary and liver mets
46	250-3535	4	14	02-10-93	04-08-93	PD	04-15-93	New subcutaneous abdominal mass and increase intraabdominal disease
47	250-3536		07					Ineligible: Pain not stabilized
48	250-3537	4	16	02-24-93	06-03-93	SD	06-03-93	New liver met
49	250-3538	4						Ineligible: Severe COPD

Appendix: JHAZ

Table II: JHAZ - Patient Treatment Evaluation

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Response	Date Off-Study	Comments
50	250-3591	3	30	02-09-93	—	PR	07-13-93	PR — Patient refused further treatment on — Progression documented on — with hepatic met
51	251-3621	4	60					Ineligible — due elevated LFTs; died from disease
52	251-3623	4	32	09-22-93	10-20-93	PD	11-10-93	New ascites —
53	251-3625	4	21	01-06-94	03-10-94	PD	03-10-94	Increase in hepatic disease
54	252-3541	4	97	04-19-93	11-24-93	PR	02-22-94	PR — with progression on —
55	252-3542	4	45	01-28-94	02-03-94	PD	03-01-94	Developed ascites — died from
56	252-3543	4	119	03-08-94	04-04-94	PD	04-04-94	Increase in all disease sites
57	253-3561	4	30	08-26-92	09-30-92	PD	09-30-92	
58	253-3562	4	28	12-08-92	03-23-93	SD	03-24-93	Progressive disease in pancreas
59	253-3563	4	28	05-05-93	05-20-93	PD	06-02-93	New ascites
60	253-3564	3	91	07-21-93	09-13-93	PD	09-13-93	Hospitalized with SBO due to progressive disease —
61	253-3565							Ineligible: No histological dx.; elevated LFTs
62	254-3591							(Incomplete CRF)
63	254-3592	4	150	03-30-93	05-25-93	PD	05-26-93	New lung lesion; Pt. lost to F/U
64	254-3593	2*	60	04-13-93	07-20-93	SD	07-20-93	Increase in primary, no evidence of nodes or mets in CRF
65	254-3594	2*	305	08-16-93	11-04-93	PD	04-25-94	Initial CT indicated 3 x 2 cm lesion; On — 4 x 4 cm.; confirmed on — Pt. on study until — when jaundice developed
66	254-3595	4	49	09-22-93	10-22-93	PD	12-01-93	New ascites on — with increase in primary
67	256-3631	4	14	11-04-92	—	SD	12-23-92	Pt. refused further therapy on — because "quality of life was decreasing due to side effects"

Table II: JHAZ - Patient Treatment Evaluation

No.	Study No.	Stage	FU Exposure (Days)	Date on Study	Date of Progression	Response	Date Off-Study	Comments
68	256-3632	4	27	05-04-93	---	NE	05-12-93	Pt. refused further therapy on "feels better off chemo"
69	256-3633	4	25	06-08-93	09-27-93	SD	10-13-93	Progressed in liver
70	256-3635	4	20	12-22-93	01-19-94	PD	01-19-94	Progression of primary and in lung
71	271-3681	4	7	02-11-94	---	NE	02-15-94	Pt. refused therapy on

Clinical Benefit Response Data

Table III: JHAZ-Clinical Course of Clinical Benefit Responders

Study No.	Objective Response	Disease Stage	CBR Parameters	Response Weeks (Duration- wks)	Comments
250-3531	PD	4	PI ↑ AC ↓ PS 70--	Wks. 3-17	On-study: 19 weeks. All treatments on schedule with reduction in wk 7 cycle 1 due to leukopenia; Cycle 3 developed g. 3 ALT, AST; No other toxicities reported. Weight down 6 kgs. on study. Developed ascites wk 3 of study, new peritoneal implants on weeks 11.
250-3537	SD	4	PI ↓ AC ↓ PS 70 ↑	Wks. 5-10 (10)	On study: 14 weeks. Cycle 1 (8 weeks), week 2 and 3 reduced 25% due to g. 2 neutropenia; Dose escalation per protocol cycle 2 and 3 with a 25% dose reduction wk. 2 cycle 3 due to g.2 neutropenia. Off study due to disease progression. Wt. up 9 kg (known liver mets but no mention of ascites)
253-3562	SD	4	PI ↓ AC ↓ PS 70 --	Wks. 3-15 (14)	On study: 16 weeks. Cycle 1 (4 weeks) with week 3 reduced 25% due to g. 2 neutropenia and leukopenia. had g.2 nausea and vomiting, g. 2 headache. Cycle 2: full dose on schedule. No toxicity. Cycle 3: dose ↓ 25% week 1,2. Dose held week 3 due to g. 2 neutropenia. No improvement in PS during course. Wt. ↓ 7 kgs. Patient did not receive any therapy weeks 11-15. Off-study due to progression.
213-3581	SD	4	PI -- AC ↓ PS 70 --	Wks. 9-12 (4)	On-study: 13 weeks. All treatments on schedule without dose escalations. Cycle 1 (8 wks): g. 1 anemia, leukopenia. Cycle 2 (4 weeks): g. 2 anemia, leukopenia, abdominal pain. New ascites and pleural effusion, g. 2 asthenia, anxiety. Cycle 3: one week only when pt. off-study due to massive ascites. Weight ↓ 5 kg. with ascites.

* Asterisk indicated a difference between applicant and reviewer in assessment of that parameter.

Table III: JHAZ- Clinical Course of Clinical Benefit Responders

Study No.	Objective Response	Stage	CBR Parameter	Response Weeks (Duration-wks.)	Comment
250-3591	PR	3	PI -- AC 1 PS 80 --	Wks. 5-12 (9)	On-study: 24 weeks. Cycle 1 (8 weeks) on schedule with g. 2 nausea and vomiting, rash and leukopenia. Cycle 2 (6 weeks) With dose 1 33% for three doses. No treatment for three weeks. G. 3 abdominal pain, g. 2 anorexia, g. 3 nausea and vomiting. Cycle 3 (3 weeks) with treatment day 1 only due to g. 2 nausea and vomiting, anorexia. Cycle 4 (4 weeks) with treatment day 1,8 only due to g. 3 nausea and vomiting, g. 3 asthenia, g. 1 leukopenia. Cycle 5. week 1 25% 1 in dose, week 2 50% 1 in dose with g.1 leukopenia. Patient refused further therapy despite PR and was noted to progress one week later. In reviewing CBR parameters pt. reported 1 PI wk. 13, 14, 19, 20, 21 with increase in analgesia consumption wk. 13-22 but remains CBR by definition. Wt. stable.
254-3594	PD	4	PI -- AC -- PS 70 1	Wks. 8-36* (29)	On-study: 36 weeks. Cycles 1-3 (16 weeks) on schedule with full dose with g.3 chills, g.2 headache only. Cycle 4 (4 weeks): 25% 1 with treatment day 1 and 8 only. Developed g. 2 abdominal pain, back pain, and GI bleeding (wk 3. held). Cycle 5 (4 weeks): same dose as C. 4 with all treatment; persistent g. 2 abd. and back pain, g.1 chills. Cycle 6 (4 weeks): 20% dose escalation per protocol, all doses on schedule with new G.3 diarrhea, other toxicities stable. Cycle 7 and 8 same dose as cycle 6. Developed 1 LFTs, g. 2 abdominal pain, g. 2 jaundice with continued pain. Weight 1 9 kg. on study. On CT scan had increasing abdominal mass after 4 wks. on study. Patient had increase pain intensity starting week 22, increased analgesia consumption starting week 23 but by definition remained CBRer.
219-3604	SD	4	PI 1 AC 1 PS 70--	Wks. 1-20 (20)	On-study: 20 weeks. Cycle 1: (8 weeks) on schedule with dose reduction 25% weeks 5,6,7 due to g. 3 asthenia with g. 2 nausea. Cycle 2: (4 weeks) with 25% dose reduction, g. 1 nausea and vomiting, g. 2 anorexia and dyspepsia; Cycle 3 (8 weeks) with treatment weeks 1-3 no treatment week 4-8 (Study weeks 16-20) with g. 1 nausea and vomiting, g. 2 anorexia, g. 2 1 in hemoglobin. No PS, PI reported week 20. Wt. 1 2 kg on study. Off-study due to liver progression.

Table III: JHAZ - Summary of Clinical Course of Clinical Benefit Responders

Study No.	Objective Response	Disease Stage	CBR Parameters	Study Weeks (Duration-Wks.)	Comments
219-3606	SD	4	PI ↓ AC -- PS 60 --	Weeks 3-18 (15)	On-study: 19 weeks. Cycle 1 (8 weeks) with no treatment weeks 7, 8 due to pneumonia. Had g. 2 leukopenia, back pain, nausea and vomiting. Cycle 2 (4 weeks) no dose escalation, all doses on schedule. G. 3 back pain, g. 2 nausea and vomiting, g. 2 rash. Cycle 3: No dose escalation, all doses on schedule with g. 2 nausea and vomiting, g. 3 back pain. Cycle 4: one dose given at 25% dose escalation. Patient hospitalized for excessive morphine use in attempt to control pain last two weeks of study. Referred for palliative RT to control pain at discontinuation from study. Weight stable.
248-3611	SD	4	PI ↓ AC -- PS 60--	Weeks 3-13 (10)	On-study: 13 weeks. Cycle 1 (6 weeks) no therapy week 5, 6 due to g. 3 neutropenia, also had g. 2 rash. Cycle 2 (4 weeks): 100% dose day 1, 8. 50% dose reduction day 15 due to g. 2 neutropenia, thrombocytopenia, g. 2 rash persisted. Cycle 3 (4 weeks): day 1 100% dose, day 8-no treatment, g. 4 neutropenia, day 15-80% dose ↓ due to g.3 neutropenia. ——— massive Gi bleed day of treatment. Wt. ↓ 4 kg.
248-3612	SD	4	PI -- AC ↓ PS 70--	Weeks 8-27 (12)	On-study: 20 weeks. Cycle 1 (8 weeks) at full dose with g.2 ALT, AST ↑. Cycle 2 (4 weeks) with day 1 100% dose, day 8 ↓ 25% and day 15 ↓ 50% due to g. 3 neutropenia. LFTs g. 1 ↑ AST. Cycle 3: day 1 full dose, day 8 held due to g. 3 neutropenia, day 15 100% dose given. Noted to have hydronephrosis. Cycle 4: day 1, 8-100% dose, day 15 no treatment due to g. 3 neutropenia, g.2 thrombocytopenia, g. 2 Hgb ↓. Cycle 5: day 1 at 100% dose with day 8 held. Found to have renal calculus. Wt. ↓ 4 kg on study.
248-3614	SD	4	PI -- AC -- PS 70 ↑	Weeks 8 --- (69)	On-study 76 weeks as of cut-off date. In the first five cycle of 4 weeks duration never had more than two treatment per cycle due to g. 3 neutropenia, g. 2 ALT ↑. G. 1-2 pain (site not specified) during these cycles. With cycle 6 doses were reduced 25% and patient was able to receive 90% of treatments with g.1-2 neutropenia, g. 1-2 anemia. Alive and well enjoying the ADLs at cut-off with PS 90-100. Wt. ↓ 2 kg. on study.

Table III: JHAY - Summary of Clinical Course of Clinical Benefit Responders

Study No.	Objective Response	Stage	CBR Parameters	Response Weeks (Duration)	Comments
248-3618	PR	4	PI -- AC -- PS 70--	Week 8-38 (31)	On-study: 40 weeks. Cycle 1 (8 weeks) 100% dose wk 1-3, 5-7; 25% dose reduction week 4 due to g. 2 neutropenia. Cycle 2 -9 (4 weeks duration) 100% dose except for two reduction of 25% week 3 of cycle 3 and 7 for g. 2 neutropenia. Developed g. 2 nausea and vomiting, g. 2-3 back pain cycles 8 and 9. Wt. ↓ 1 kg on study. Had lumbar met on CT and was taken off study at end of cycle 9.
248-3619	SD	4	PI ↓ AC -- PS 70 --	Weeks 1-18 (18)	On-study: 19 weeks. No CBR data week 19. No PS week 5, 6. Cycle 1 (7 weeks), treated weeks 1-5 on schedule at 100% dose. Hospitalized → due to g. 3 nausea and vomiting, also g. 1 anemia, g. 2 leukopenia during first cycle. Cycle 2: (4 weeks) treated at full dose on schedule (no escalation) with g. 2 nausea and vomiting. Cycle 3 (4 weeks): day 1, 8-100% dose on schedule, day 15 25% dose ↓ due to g. thrombocytopenia. G. 1 leukopenia, g. 2 nausea, g. 2 abdominal pain noted. Cycle 4 day 1, 8 treatments only at 100% dose. G.2 abdominal pain, g. 2 nausea. Developed ascites, and developed DVT. Wt. ↓ with ascites.
248-3620	SD	4	PI ↓ AC -- PS 70 --	Weeks 2-12 (11)	On-study: 12 weeks. Cycle 1 (9 weeks) 100% of dose with g. 1 neutropenia, grade 1 fever, one grade 1 in ALT and AST. Cycle 2 (4 weeks) 25% ↓ with all doses on schedule, g. 3 neutropenia, g. 2 fever. Wt. ↓ 2 kgs.
248-3675	SD	4	PI ↓ AC -- PS 70 ↓	Weeks 4-41 (38)	On study: 42 weeks. Cycle 1 (6 weeks), 100% dose week 1, 2 25% ↓ week 3 due to g. 2 neutropenia, 50% ↓ week 4 due to g. 2 neutropenia, no treatment week 5, 6 due to g. 3 neutropenia. Also had g. 2 Hgb ↓; g. 1 ALT ↑. Cycle 2 (4 weeks): 100% dose on schedule, no toxicities reported. Cycle 3 (4 weeks): 25% dose escalation with g. 2 neutropenia and Hgb. ↓; Cycle 4 (4 weeks): same dose as cycle 3 on day 1, 8. No treatment day 15 due to g. 3 neutropenia. Cycles 5-9: (4 weeks) no further dose escalation, all treatments on schedule. In cycle 10 developed g. 2 thrombocytopenia, g. 1 neutropenia, g. 1 ALT, AST ↑ and g. 2 back pain. Patient off study due to new pulmonary mets. Wt. gain 2 kg. on study. In reviewing the date, this patient is not a CBRer until wk 9. when the PS ↓ to 90 as the AC was less than 30 on study and PI less than 20 at baseline, stable by definition.

Table III: JHAZ - Summary of Clinical Course of Clinical Benefit Responders

Study No.	Objective Response	Stage	CBR Parameter	Response Weeks (Duration)	Comments
248-3678	SD	4	PI 1 AC -- PS 70--	Weeks 1-10 (10)	On-study: 16 weeks. No CBR data weeks 11-16. Cycle 1 (6 weeks): Week 1-4 100% dose on schedule; Week 5 not treatment due to g. 3 neutropenia; weight loss 5 kg. cycle 1. Cycle 2 (4 weeks) with day 1, 8 on schedule; no treatment day 15 due to g. 2 neutropenia, g. 2 diarrhea. Cycle 3 (4 weeks): Treated day 1 only due to g. 3 neutropenia, g. 3 asthenia, g. 3 flu-like syndrome. Patient died from disease on study. Wt. ↓ 1 kg.
248-3679	SD	4	PI -- AC ↓ PS 70↓	Weeks 2-37 (36)	On-study: 37 weeks. Cycle 1 (8 weeks): dose ↓ 25 % week 2 due to g. 2 thrombocytopenia; no other toxicities noted. Cycle. 2-5 (4 weeks/cycle); dose reduction 25 -50% due to g. 3 thrombocytopenia and in cycle 5 g. 2 neutropenia. Cycle 6-8 (4 weeks/cycle): Two treatments / cycle with 25% dose reduction due to g. 3 thrombocytopenia. Cycle 9: one dose only due to thrombocytopenia. Received Procrit for anemia on last cycle. Had g. 1 abdominal pain cycle 8, 9. Wt. ↓ 8 kgs. on study.

Table IV: JHAZ-Study Discontinuations due to Adverse Events

- 210-3553 Stage IV disease with known hepatic mets. On study 3 weeks with three injections in the first cycle. Developed asthenia, dehydration, fever, nausea and vomiting, somnolence, and mental status changes at which time patient refused further therapy. Died _____ later from disease progression. Death is disease related. Discontinuation appears due to a combination of disease progression and study drug toxicities.
- 248-3572 Sage II disease with a history of portal hypertension, pedal edema, and chronic bronchitis. On study for five weeks with treatment weeks one, two (dose 2 ↓ 25% for gr. 2 neutropenia and thrombocytopenia), week three held,; week four and five given at full dose. Had disease progression with development of jaundice and ascites on study. Other complaints included gr. 2 myalgia, gr. 3 syncope, gr. 3 asthenia. Patient died on study from progressive disease.
- 248-3616 Stage IV disease. On study for 49 days with no treatment after day 8. Patient developed

hepatic abscess and Clostridium sepsis at day — No evidence of myelosuppression when abscess developed. At time of I & D of hepatic abscess ascitic fluid positive for malignant cells. Patient stabilized for — then developed DVT. Died suddenly from complications of disease.

- 248-3611 Stage IV disease. On study 13 weeks, clinical benefit responder week 3 to 13. In first cycle (6 weeks) dose 5 omitted due to gr. 3 neutropenia, gr. 3 leukopenia and gr. 3 rash. In cycle 2 (4 weeks) injection 3 omitted due to gr. 2 leukopenia and neutropenia. In cycle 3 had day 15 dose reduced due to leukopenia and neutropenia with a normal platelet count. — dose died from massive GI bleed. Had been placed on NSAIA three days before death. CT day of death showed progression. Death is disease related.
- 248-3678 Stage IV disease. On-study: 16 weeks. Is a clinical benefit responder weeks 1-10. In the first cycle (6 weeks) had four doses, with fifth omitted due to gr. 3 neutropenia and leukopenia. In cycle 2 (4 weeks) had treatment weeks 1 and 2 due to gr.2 neutropenia. In cycle 3 the first dose was given with a 25% dose reduction in spite of which the patient developed gr. 3 leukopenia and neutropenia. Complained of gr. 3 asthenia and gr. 3 flu-like syndrome. Patient was hospitalized week 13 due to severe fatigue and discharged to hospice care. Study discontinuation due to progressive disease.
- 248-3680 Stage III disease. Had one cycle (6 weeks) with six injections. Had 25% dose reductions week 3, 4 due to gr. thrombocytopenia and anemia (not reported in toxicity section). Had a decrease in hemoglobin from gr.1-3 and elevation in ALT and AST to grade 2. Died from a Gi bleed day. — of study from Gi bleed. Death is disease related. Platelet count not reported.
- 219-3606 Stage IV disease. On study: 19 weeks. Clinical benefit responder weeks 3-18. During cycle 1 (8 weeks) received six of seven injections with the seventh held for pneumonia (gr. 2 neutropenia reported cycle 1). During cycle 2 and 3 had full doses on schedule. had gr. 3 abdominal and back pain, gr. 2 nausea and vomiting, and gr. 2 rash. During week 2 and 3 of cycle 4 patient was hospitalized for treatment of morphine overdose secondary to intolerable abdominal and back pain. The patient was discontinued from study and referred for palliative RT when analgesics were unsuccessful in controlling pain. Discontinuation is due to disease related symptoms.

Appendix: JHAZ

Table V: Internal Review of Reported Complete and Partial Responses - JHAZ

All CTs and Ultrasounds forwarded by the applicant were reviewed by Dr. Joseph Pierro (HFD-160) to determine why a discrepancy occurred between the individual investigator assessment and the Eli Lilly sponsored independent Review Board assessment. Dr. Pierro's assessment of response is as follows:

- 248-3675: Unable to clearly delineate the pancreas and the clearly define the lesion, therefore response assessment is difficult
- 252-3541 No evidence of any change in size of lesion between initial scan and those of — and —
—
- 254-3591 No difference between the two scans submitted for review
- 248-3619 Appears that patient had a drainage procedure between initial scan on — and follow-up on — Mesenteric inflammation and ascites are noted on — and no improvement is noted in the region of the pancreas. Pancreatic duct is dilated.
- 248-3618 Lesion in tail of the pancreas which did not appear to decrease in size on follow-up scans
- 248-3678 Pancreatic mass with liver metastases; FU —, poorly visualized but are present and unchanged in size

VIII: PHASE II SUPPORTING STUDIES

Preface:

At the pre-NDA meeting held in November, 1994 the applicant was requested to submit two phase II studies (JHAL, ext. and E012) in which gemcitabine was used on the same dose /schedule in previously untreated pancreatic cancer patients. More information would then be available about the response parameters and the toxicity profile of gemcitabine in advanced pancreatic cancer. The sponsor also submitted a study report for JHAL which will be reviewed briefly for efficacy and toxicity.

In the first study, JHAL,ext. (which uses the same protocol as JHAL with an amended dosing schedule) response rates, time to progression, time to treatment failure, and survival can be determined. In the second study, E012, tumor response, time to treatment failure, and time to progression as well as toxicity can be assessed. The dosing schedule in JHAL is the same as the dosing schedule in JHAY and JHAZ. The dosing schedule in E012 is 800-1000 mg/m² weekly for three weeks of a four week cycle.

I. REVIEW OF JHAL, ext.:

Title: Gemcitabine (DFDC) - Phase II - Weekly x 3 Every 4 Weeks in Patients with Pancreatic Cancer

Protocol Summary:

Design: Multicenter, open-labeled, non-randomized study

Dosing Schedule:

Cycle 1: 1000 mg/m² weekly x 7 with week 8 rest

Cycle 2: 1250 mg/m² (25% ↓) weekly x 3 with week 4 rest if no hematological toxicity and no other toxicity greater than grade 1

Cycle 3: 1500 mg/m² weekly x 3 with week 4 rest if no hematological or other toxicity greater than grade 1

Dose Adjustments:

Toxicities are graded using the WHO Toxicity Criteria with dose adjustments as follows:

Hematological toxicity:

AGN >1500/ul	and platelets > 100,000/ul	- 100% dose
AGN 1000 -1499/ul	or platelets 50 - 99,000/ul	- 50%↓ dose
AGN 500 - 999/ul	or platelets 25 - 49,900/ul	- Hold*
AGN < 500/ul	or platelets < 25,000/ul	- Hold*

(* amended to reduce dose 50% next cycle on November 17, 1989)

Non-Hematological Toxicities:

Grade ≤ 2 (except skin rash)	- 100% dose
Grade 3 (except grade 1, 2 skin rash)	- 50% dose**
Grade 4 (or grade 3 skin rash)	- HOLD**

No doses were to be made up. For subsequent cycles of therapy the following dose modifications apply:
For Hematologic Toxicity During the Previous Cycle:

AGN > 1500/ul	and Platelets >150,000/ul	- Dose \uparrow 25%
AGN 1000 - 1499/ul	and Platelets 100 -149,000/ul	- Same*
AGN 500 - 999/ul	and Platelets 50 - 99,900/ul	- Same
AGN < 500/ul	and Platelets < 25,000/ul	- 50% \downarrow Dose

For Non-Hematologic Toxicity during the Previous Cycle:

Grade 0-1	escalate dose 25%
Grade 2 (or grade 1 skin rash)	same dose
Grade 3 (or grade 2 skin rash)	same dose
Grade 4 (or grade 3 skin rash)	reduce dose 50% or stop

Eligibility Criteria:

Inclusion criteria for this study include:

Histological or cytological diagnosis of pancreatic cancer with recurrent and/or advanced disease not curable by surgery or radiotherapy

No history of prior chemotherapy;

Previous radiotherapy to area non-evaluable for response allowed

Performance status: 0-1

Measurable disease

Estimated life expectancy of twelve weeks

Patient compliance

No treatment with radiation or steroids within three weeks of study entry

Adequate bone marrow reserve: WBC \geq 3500/mm³,

Platelets \geq 100,000/mm³,

Hematocrit \geq 30%

Hgb \geq 10 g/dl,

Age \geq 18 years

For females, proof of permanent termination of childbearing potential or attenuation by use of approved contraceptives

Signed informed consent

Exclusion Criteria for this study include:

History of other malignancy within 5 years except recently resected basal cell carcinomas or cervical cancer \leq stage I curatively resected

Active infection

Prior brain radiation for CNS metastases

Concomitant radiotherapy, chemotherapy, hormonal, or immunotherapy

Inadequate liver function: Bilirubin $>$ 1.5 mg/dl and/or SGOT $>$ 3 times normal, PT $>$ 1.5x control, aPPT $>$ 1.5x control, SGOT and/or SGPT $>$ 5x normal

Inadequate renal function: creatinine $>$ 1.5 mg/dl

Calcium $>$ 10.5 mg%

Inadequate contraception

Breast Feeding

Active cardiac disease requiring therapy for angina and/or arrhythmias; non-compensated failure on therapy; myocardial infarction within 6 months; severe pulmonary disease; significant peripheral vascular disease; significant neurological or psychiatric disorders

Clinical and Laboratory Parameters Used for Efficacy and Toxicity Measurements:

History, PE on study and monthly

Wt., Ht., and PS on study and weekly

CEA on entry and q 4 weeks

Chest x-ray (PA and Lateral) on entry and q 8 weeks

WHO toxicity evaluation at baseline and weekly

CT, MRI, Ultrasound, or Liver-Spleen Scan

Analgesia Scores weekly

0 = None

1 = ASA, acetaminophen

2 = Codeine, Propoxyphene

3 = Oral dilaudid, morphine sulphate, methadone, percodan

4 = Parental opiates

5 = Neurosurgical procedures

CBC with diff, platelets, PT, aPTT on entry and weekly

Blood chemistries: creatinine, BUN, bilirubin, alkaline phosphatase, SGOT, SGPT, glucose, electrolytes, calcium, total protein, albumin, phosphorus, uric acid weekly

U/A weekly

EKG on study and monthly

Post-study followup of any abnormality related to study drug

Patient Disposition: Reasons for Study Terminations:

Definite evidence of progressive disease

Physician judgement

Patient request

Unacceptable drug toxicity

Sponsor's discretion

Efficacy Criteria:

Complete Response: disappearance of all clinical evidence of active tumor for a minimum of four weeks with the patient free of all tumor related symptoms

Partial Response: fifty percent or greater decrease in the sum of the products of all diameters of measurable lesions for a minimum of four weeks

Stable Disease: decrease in tumor mass less than 50% in the sum of the products of the diameters of the measurable lesions or an increase in tumor mass less than 50% in the absence of the development of new lesions

Progressive Disease: Increase in the sum of the products of the diameters of the measurable lesions (50%) or the appearance of any new lesion

Study Results:

Patient Demographics:

Case records were submitted on forty-four patients. The disposition of these patients is as follows:

Objective Progression.....	34
Death on Study.....	3
Disease-related.....	1
Other causes.....	2
Treatment Failures.....	8
Drug Related Renal Dysfunction.....	1
Patient Refusal.....	2
Abnormal Liver Function with therapy..	1
Cachexia, Tumor-related.....	1
Elevated LFTs, no therapy.....	2

The demographic data of the study population is shown below:

	Parameter	Number (Per Cent)
Sex	Female.....	15 (34.1)
	Male.....	29 (65.9)
Race	African Descent.....	1 (2.3)
	White.....	42 (95.5)
	Hispanic.....	1 (2.3)

Age

Median.....62.5 yrs
Range..... (44- 82 yrs)

Stage

II.....2 (4.5)
III.....1 (2.3)
IV.....41 (93.3)

Performance Status

0.....6 (13.6)
1.....38 (86.4)

Level of Analgesia

0.....5 (11.4)
1.....8 (18.2)
2.....12 (27.3)
3.....17 (38.6)
4.....0
5.....2 (4.5)

Time for Diagnosis

Median.....1.1 mos.
Range.....(0.1-8.2 mos.)

Patients On Study Per Cycle

Cycle 1.....41
Cycle 2.....27
Cycle 3.....22
Cycle 4.....14
Cycle 5.....11
Cycle 6.....9
Cycle 7.....6
Cycle 8, 9.....2

In this study 61.3% of the patients were reported on study after one cycle as compared to 53.9% in JHAY, 50% of the patients remained on study after cycle 2 in this study as compared to 41.2% in JHAY. The number of patients with advanced clinical disease stage in this trial is greater than in JHAY. No other differences in demographic data is noted.

Tumor Response Parameters:

Objective Response Rate

After reviewing the CRFs the following response rate is observed:

Complete.....	1 (2.3%)
Partial.....	1 (2.3%)
Stable Disease.....	22 (50.0%)
Progressive Disease.....	14 (31.8%)
Nonevaluable.....	6 (13.6%)

The 95% confidence interval around the response rate is 0 - 11%. All responses were confirmed by an external Oncology Review Board. The complete response was noted one month after initiation of therapy and was sustained for 4.6 months. The partial response occurred at one month after entry and was sustained for 7.4 months.

Time to Progression Analysis

Time to progression is the time from date of first treatment to date of progression. Six patients were not evaluable for response and four patient (10.8%) were censored in this intent to treat analysis. The median time to progression is 85 days with a range of 0-244+ days. The 95% confidence interval around the time to progression is 56-105 days.

Time to Treatment Failure

Forty-three patients were evaluable for time to treatment failure using intent to treat analysis. One patient was not treated. The median time to treatment failure is 57 days (95% confidence interval: 29-85 days) a range of 0 - 244+ days. The 95% confidence interval around the time to treatment failure is 27-85 days. The shorter median time to treatment failure is due to the three deaths on study, one patient refusal to continue treatment, and one study discontinuation due to an adverse event.

Survival

Six patients (14%) were censored in this analysis. Median survival was 103 days (95% confidence interval: 49-128 days) with a range of 0-275 days.

Safety Analysis

(In this protocol three patients were started at the 800 mg/m² dose level. When no myelotoxicity was observed, the dose was increased to 1000 mg/m² weekly for seven weeks with a week eight rest.)

Deaths

Three deaths occurred on study none of which was due to drug.

Hospitalizations

Twelve patients were hospitalized for a total of twenty-one times. The reasons for hospitalization are listed below:

Reason	Number
Disease Related.....	7
Drug Related.....	6
Chills.....	1
Nausea and Vomiting.....	4
Pancytopenic Fever.....	1
Neutropenic Fever.....	1
Possibly Drug Related.....	1
Bilateral Pulmonary Infiltrates.....	1
Others.....	7
Vomiting with Pyloric Stenosis.....	1
Peritonitis.....	1
DVT.....	3
Klebsiella sepsis.....	1
Hyperkalemia.....	1

Study Discontinuations for Adverse Reactions

One patient (210-1236) with stage II disease developed hematuria and proteinuria during cycle 3 which persisted and worsened throughout study. Myelosuppression was noted during cycle 3 with gr. 2 Hgb toxicity, gr. 2 leukocyte, and gr. 3 neutrophil toxicity. Intermittent myelosuppression with recovery after dose reductions and omissions occurred during subsequent cycles. The patient became more anemic (Hgb -7.7 gm%) and required transfusion of two units packed RBIS during week 35 of therapy. Pedal edema developed. Hypertension was noted during week 37 along with elevation of the creatinine and worsening hematuria. Patient was treated for two more weeks but was taken off study with dyspnea, hypertension, gr.1-2 ALT, AST, Hgb-6.1 gm%, AGN -1012/ul, and platelets -48,000/ul The patient was felt to have a variant of the hemolytic uremic syndrome.

In two cases (209-1246 210-1322) patients refused further therapy. In one patient (209-1246) the drug toxicity was minimal. In the second (210-1322) the patient refused further therapy due to "decrease in the quality of life". Toxicities for this patient included: hematuria, proteinuria, edema, anorexia and weight loss requiring hospitalization. While tumor may have caused the some symptoms, therapy appears to have exacerbated them.

Dose Omissions, Reductions, and Escalations

In this study 526 injections were scheduled with 497 (94.4%) injections administered. Of the injections given, 289 (54.8%) were given on schedule, 161 (30.6%) were escalated, 48 (9.1%) were reduced, and 29 (5.5%) were omitted. The reasons for the dose reductions and omissions were hard to analyze due to

the method of reporting. Of those omitted doses seven omissions were known to be due to neutropenia and thrombocytopenia, three doses were omitted for unexplained fever, one omission was for nausea and vomiting, and one was due to severe edema while the other omissions were for miscellaneous reasons.

Treatment Related Signs and Symptoms

The number of patients reporting treatment related signs and symptoms (TESS) are recorded in the following table. Those signs and symptoms which are definitely related to tumor are omitted. About 50% of the patients develop a constellation of symptoms related to the "flu-like" syndrome including headache, chills, fever, myalgia, and fatigue and one, more than one, or just "flu-like" syndrome might be reported.

Table 1: Treatment Emergent Signs and Symptoms

Parameter	No. of Patients (Total = 44)	Per Cent
Asthenia	31	70.5
Fever	22	50.0
Neutropenic Fever	2	
Sepsis*	2	
Chills	10	22.9
Headache	5	11.4
Flu Syndrome	2	4.5
Anorexia	15	34.1
Nausea	25	56.8
Vomiting	22	50.0
Diarrhea	12	27.3
Stomatitis	1	2.3
Dehydration	4	9.1
Edema	8	18.2
Peripheral Edema	8	18.2
Myalgia	8	18.2
Dyspnea	5	11.4
Rash	9	20.5
Alopecia	5	11.4
Taste Perversion	2	4.5

*One case of sepsis was associated with neutropenia.

The incidence of treatment related symptoms and signs which appear to be drug related in this study is similar to the incidence reported in other trials and in order of frequency include: asthenia - 70%, nausea -

56.8%, vomiting - 50%, anorexia - 34.1%, edema - 18-36%. Patients on therapy with gemcitabine may complain of generalized weakness or asthenia due to drug and not related to the underlying malignancy.

Incidence of Toxicity by Grade:

In this portion of the review toxicities will be reported by grade with the worst grade for any cycle for each patient reported in tabular form. Only toxicities related to or possibly related to drug will be presented in this table.

Table 2: WHO Grading for Drug Related Laboratory Toxicity

Parameter	No. of Patient per Cycle	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	41	8	16	11	3	3
White Blood Count	41	21	6	8	3	3
Neutrophils	41	17	6	8	4	6
Platelets	41	30	4	5	1	1
Proteinuria	39	7	27	5	0	0
Hematuria	39	18	14	7	0	0
Creatinine	41	38	3	0	0	0
ALT	14	4	5	3*	1*	1*
AST	40	7	15	10	3*	5*

In those cases where the AST or ALT is asterisked, elevation is due to drug toxicity, not metastatic disease.

Table 3: Hematologic Toxicity by Cycle (Cycles 1-4)

Parameter	Cycle 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4
No. of Patients / Cycle	44	41	27	22	14
Hemoglobin					
Gr. I	6	19	12	9	4
Gr. II	1	8	5	1	6
Gr. III	0	2	2	4	3
Gr. IV	0	1	0	0	1
Neutrophils					
Gr. I	0	6	6	2	3
Gr. II	0	7	3	2	3
Gr. III	0	3	3	4	2
Gr. IV	0	5	0	1	0
Platelets					
Gr. I	0	3	2	1	0
Gr. II	0	4	1	0	1
Gr. III	0	0	1	1	0
Gr. IV	0	1	0	0	0

Nine patients (20.5%) were transfused red cells. No patients had platelet transfusion. One patient had neutropenic sepsis and one patient had neutropenic fever. About two-thirds of the patients develop anemia, about half neutropenia (mild, non-sustained), and a few thrombocytopenia. As noted above one patient in this study had a variant of the hemolytic-uremic syndrome.

Table 4: Non-Hematologic Toxicities - Worst Grade per Patient

Parameter	No. at Risk	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous Lesions (Low dose steroids allowed for rash while on study)	41	27	9	4	1	0
Alopecia	41	36	5	0	0	0
Fever	40	19	9	10	3	0
Infections	41	34	2	1	1	1 Peritonitis
Allergic Reactions	41	41	-	-	-	-
Pulmonary (No cases of Bronchospasm)	44	37	1	3	0	0
Gastrointestinal						
Mucositis	41	39	2	0	0	0
Nausea & Vomiting	41	6	21*	11	2	0
Diarrhea	41	25	9*	5*	2*	0
Neurotoxicity	41	29	7	4	1	0

* One patient in each group had grade I diarrhea at entry.

** Fifteen patients had grade I nausea and vomiting, eight were stable on therapy, four worsened to grade II, and one worsened to grade 3.

Summary

In this phase II study forty-four patients were entered. One complete response lasting 4.6 months and one partial response lasting 7.4 months were observed. The median time to progression was 85 days (range: 0 - 244+ days) and the median time to treatment failure was 57 days (range: 0 -244+ days). Median survival time was 103 days (range: 0 - 275 days). The principal toxicities include: asthenia (70%), nausea (56.8%), vomiting (50%), fever (50%), anorexia (34%), diarrhea (27.3%) and rash (20.5%). Fever without infection or neutropenia was observed in nineteen patients.

Myelotoxicity including anemia, leukopenia with neutropenia, and thrombocytopenia was reported with the majority of cases was grade 1-2. Elevation of liver function studies of grade III/IV was observed during the first few cycles but resolved. No patients were removed from study due to liver toxicity. One patient developed a variant of the hemolytic-uremic syndrome and was removed from study. No allergic reactions were reported, however five patients developed treatment related rash of grade 2-3. Five patients had dyspnea which resolved and no patient was removed from study due to this pulmonary toxicity.

Appendix: JHAL , ext.

Table 1: Patient Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date of Death	Response	Comments
1	209-1241	4	07-30-91	11-18-91	—	SD	Died of Disease
2	209-1242	4	08-02-91	11-21-91	—	SD	
3	209-1243	4	08-01-91	—	—	NE	No treatment, removed from study on — due to poor condition; received other therapy
4	299-1244	4	08-06-91	11-23-91	—	PD	Off-study due to progression
5	209-1245	4	08-14-91	12-08-91	—	SD	Off-study due to progression
6	209-1246	4	08-13-91	—	—	SD	Pt. refused further treatment
7	209-1247	4	08-20-91	03-30-92	—	PR	Died from disease
8	209-1248	4	08-27-91	12-17-91	—	SD	Died from disease
9	209-1249	2	09-10-91	12-24-91	—	SD	Died from disease
10	209-1250	4	10-24-91	02-06-92	—	SD	Died from disease
11	209-1351	4	10-17-91	01-29-92	—	SD	New liver lesion on —; Off study on 5-12-92; Died from disease
12	209-1352	4	10-17-91	—	—	SD	Pt. developed elevated LFTs, CT showed stable disease on —, date off-study; Died from disease
13	209-1353	4	10-17-91	06-03-92	—	PD	
14	209-1354	4	10-15-91	01-14-92	—	PD	Developed biliary obstruction on —
15	209-1355	4	10-24-91	01-09-92	—	PD	Developed ascites on — Off-study 4-9-92; died from disease
16	209-1356	4	10-24-91	01-16-92	—	SD	Developed ascites — Off-study on 1-16-92

Table 1: JHAL - Patient Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date of Death	Response	Comments
17	209-1357	4	11-05-91	11-16-91	————	PD	Increased ascites; Died from disease
18	209-1358	4	11-12-91	01-24-92	————	SD	Increase in nodes; Died from disease
19	209-1359	4	11-12-91	03-03-92	————	SD	Progression in liver; died from disease
20	209-1360	4	11-21-91	12-23-91	————	PD	Died from disease
21	209-1361	4	12-19-91	02-13-92	————	PD	Died from disease
22	209-1362	4	12-19-91	02-06-92	————	PD	Died from disease
23	209-1363	4	01-07-92	03-02-92	————	PD	Increase in primary and liver; died from disease
24	209-1364	4	01-10-92	02-05-92	————	PD	New liver mets; died from disease
25	209-1365	4	01-14-92	04-29-92	————	SD	Progression of liver mets.
26	209-1366	4	01-22-92	02-18-92	————	PD	Progression of primary and liver mets; Died on study from disease.
27	209-1367	4	01-16-92	06-09-92	————	SD	New lung met on ———, Off-study on 10-22-92.
28	209-1368	4	01-06-92	—	————	NE	Admitted ——— with severe dehydration, cause of death unclear
29	209-1369	4	01-21-92	03-10-92	————	PD	Progression all sites; Died from disease
30	209-1370	4	01-21-92	05-12-92	————	SD	Progression in liver; died from disease
31	210-1231	4	04-22-91	05-02-91	————	NE	New ascites ———, died from disease
32	210-1232	4	04-22-91	08-19-91	————	SD	Had RT pre-study; Increase in liver mets ——— died from disease
33	210-1233	4	05-02-91	09-27-91	————	SD	Liver progression; On study until ——— died ———

Table I: JHAL - Patient Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date of Death	Response	Comments
34	210-1234	4	05-23-91	---	---	NE	Abnormal LFTs- Ineligible; died from disease
35	210-1235	4	06-04-91	---	---	NE	DOS: Perforated duodenal ulcer with peritonitis
36	210-1236	2	06-06-91	----	---	SD	Off-study due to A: Renal toxicity due to drug
37	210-1237	4	05-20-91	---	---	NE	Ineligible due to elevated bilirubin
38	210-1238	4	06-26-91	08-20-91	---	PD	Increase in omental disease; died from disease
39	210-1239	4	07-25-91	08-17-91	---	PD	Died from disease
40	210-1240	4	08-05-91	10-03-91	---	PD	Developed ascites : --- Died from disease
41	210-1321	3	08-07-91	10-31-91	---	SD	New lung nodule --- Off-study 2-27-92; died from disease
42	210-1322	4	11-08-91	---	---	SD	Pt. refused further therapy due to decrease in "quality of life".
43	210-1323	4	11-27-91	04-13-92	---	SD	Increase liver mets; died from disease
44	210-1324	4	02-06-92	05-04-92	---	SD	Increase in primary and new add. mass; Off-study on-7-2-92; died from disease

Table II: JHAL - Tumor Response Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date Off-Study	Response	Comments
1	209-1241	4	07-30-91	11-18-91	11-18-91	SD	
2	209-1242	4	08-02-91	11-21-91	11-21-91	SD	No treatment
3	209-1243	4	08-01-91	---	08-08-91	NE	Removed due to poor condition;
4	299-1244	4	08-06-91	11-23-91	12-05-91	PD	Off-study due to progression
5	209-1245	4	08-14-91	12-08-91	12-08-91	SD	Off-study due to progression
6	209-1246	4	08-13-91	---	10-08-91	SD	Pt. refused further treatment
7	209-1247	4	08-20-91	03-30-92	03-30-92	PR	PR — progressed in liver
8	209-1248	4	08-27-91	12-17-91	01-07-92	SD	
9	209-1249	2	09-10-91	12-24-91	12-24-91	SD	
10	209-1250	4	10-24-91	02-06-92	02-06-92	SD	
11	209-1351	4	10-17-91	01-29-92	05-12-92	SD	New liver lesion on —
12	209-1352	4	10-17-91	---	11-07-91	SD	Pt. developed elevated LFTs, CT showed stable disease on 11-07-93
13	209-1353	4	10-17-91	06-03-92	06-04-92	PD	
14	209-1354	4	10-15-91	01-14-92	01-15-92	PD	Developed biliary obstruction
15	209-1355	4	10-24-91	01-09-92	04-09-92	SD	Developed ascites on —
16	209-1356	4	10-24-91	01-16-92	01-16-92	SD	Developed ascites —

Table II: Tumor Response Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date Off-Study	Response	Comments
17	209-1357	4	11-05-91	11-16-91	11-16-91	PD	Increased ascites
18	209-1358	4	11-12-91	01-24-92	02-04-92	SD	Increase in nodes
19	209-1359	4	11-12-91	03-03-92	03-10-92	SD	Progression in liver
20	209-1360	4	11-21-91	12-23-91	12-23-91	PD	
21	209-1361	4	12-19-91	02-13-92	02-13-92	PD	
22	209-1362	4	12-19-91	02-06-92	02-20-92	PD	
23	209-1363	4	01-07-92	03-02-92	03-05-92	PD	Increase in primary and liver
24	209-1364	4	01-10-92	02-05-92	02-11-92	PD	New liver mets
25	209-1365	4	01-14-92	04-29-92	05-05-92	SD	Progression of liver mets
26	209-1366	4	01-22-92	02-18-92	04-04-92	PD	Progression of primary and liver mets; DOS: disease
27	209-1367	4	01-16-92	06-09-92	10-22-92	SD	New lung met on _____
28	209-1368	4	01-06-92	---	02-01-92	NE	Admitted _____ with severe dehydration, cause of death unclear.
29	209-1369	4	01-21-92	03-10-92	03-17-92	PD	Progression all sites
30	209-1370	4	01-21-92	05-12-92	05-19-92	SD	Progression in liver
31	210-1231	4	04-22-91	05-02-91		NE	New ascites _____
32	210-1232	4	04-22-91	08-19-91	11-27-91	SD	Had RT pre-study; Increase in liver mets _____
33	210-1233	4	05-02-91	09-27-91	12-05-91	SD	Liver progression

Table I: JHAL - Response Data

No.	Study No.	Stage	Date of Treatment	Date of Progression	Date Off-Study	Response	Comments
34	210-1234	4	---	---			Abnormal LFTs- Ineligible; died from disease
35	210-1235	4	06-04-91	---	06-12-91	NE	DOS: Perforated duodenal ulcer with peritonitis
36	210-1236	2	06-06-91	---	03-09-92	SD	Off-study due to A: Renal toxicity due to drug
37	210-1237	4	---				Ineligible due to elevated bilirubin
38	210-1238	4	06-26-91	08-20-91	08-27-91	PD	Increase in omental disease
39	210-1239	4	07-25-91	08-17-91	08-21-91	PD	
40	210-1240	4	08-05-91	10-03-91	01-13-92	PD	Developed ascites
41	210-1321	3	08-07-91	10-31-91	02-27-92	SD	New lung nodule
42	210-1322	4	11-08-91	---	01-02-92	SD	Pt. refused further therapy due to decrease in quality of life
43	210-1323	4	11-27-91	04-13-92	04-13-92	CR	Increase liver mets
44	210-1324	4	02-06-92	05-04-92	07-02-92	SD	Increase in primary and new abd. mass

II. Review: Study E012

Title: Gemcitabine (Difluorodeoxycitidine) Phase II Study in Patients with Pancreatic Cancer

Introduction:

This phase II open labelled study of gemcitabine in previously untreated patients with locally advanced or metastatic pancreatic cancer was conducted in two centers in England and one in Germany. Thirty-four patients were enrolled.

Protocol Design:

Since the protocol design for this study is very similar to that of JHAL, ext. only differences will be reviewed in this section. Dosing schedule was initially 800 mg/m² weekly x 3 every four weeks (cycle=4 weeks). After four patients were enrolled and no serious toxicity was observed, the starting dose was escalated to 1000 mg/m². Twenty-nine patients were entered on study at this dose level. An amendment was to allow dose escalation to 1200 mg/m² in patients who did not demonstrate toxicity was added in June, 1990.

Results:

Patient Demographics:

Demographics features for this study population are as follows:

Sex

Female.....	12 (35.3%)
Male.....	22 (64.7%)

Age

Median.....	55.5 yrs.
Range.....	(39 - 72 yrs.)

Stage

II.....	3
III.....	8
IV.....	22
Unknown.....	1

Performance Status

Unknown.....	1
Level 0.....	3
Level 1.....	26

Level 2..... 4

Level of Analgesia

Unknown..... 1

Level 0..... 3

Level 1..... 26

Level 2..... 4

The median age in this study is slightly less than in the other studies. In this group two patients had prior hormonal therapy -one with steroid and one with tamoxifen. No patient had received radiation therapy. About one-fifth had various types of palliative surgery.

Patient Disposition

Thirty-four patients were entered on study. Reasons for discontinuation are listed below. One patient did not receive any treatment due to poor physical condition. One patient was removed from study after one treatment due to abnormalities in lab data (The patient's entry labs were done greater than 3 weeks before entry onto study. Follow-up lab results received after the first treatment revealed new abnormalities. This patient's course is discussed in the Study Discontinuation section.)

Deaths on Study..... 2
 With therapy..... (2)
Patient Deterioration..... 5
Ineligible after therapy initiated..... 1
Clinical deterioration..... 5
Progressive Disease..... 21

Study Considerations

The cut-off date for this study was March 1, 1994 while the last patient was entered in September, 1992. Only data obtained from patients while on study is used in the data sets. As a result the number of censored data points is increased, the confidence intervals are wider and the median may not exist in the sponsor's data. The review will focus on the response rates, time to progression, time to treatment failure, and the toxicity profile. Due to the large number of censored patients (no information on date of death) survival data is not very meaningful.

Objective Response Rates

In reviewing the response data, the sponsor required the patients to be on study for 56 days (two cycles) to be eligible for response evaluation. As a result twelve patients were not eligible for response evaluation. In reviewing the case report forms, if evidence of progressive disease was noted regardless of the time on study, the patient was classified as progressive disease. If the patient did not have follow-up for disease at eight weeks or objective evidence of progression, the patient was considered non-evaluable (NE). Hence, the response rates contained in this review are slightly different from those of the sponsor.

Complete Response.....	0
Partial Response.....	2 (5.8%)
Stable Disease.....	8 (23.5%)
Progressive Disease.....	19 (55.9%)
Not Evaluable.....	5.(14.7%)

Two partial responses were identified in this study and confirmed by an external Lilly sponsored Oncology Review Board. One partial response was of 5.2 months duration, the second was of greater than 5.5 months (the patient refused further therapy after 5.5 months).

Time to Progression

Time to progression is the time from first treatment to time of evidence of progression. Five patients were not evaluable for time to progression analysis. Seven patients (25%) out of the twenty eight were censored for the following reasons: (1) patient refusal in five cases (one patient had hematuria, proteinuria 3+), and (2) clinical progression in two cases. The median time to progression was 51.5 days (95% confidence intervals: 49 - 107 days) with a range from 0 - 200 days for time to progression.

Time to Treatment Failure

Median time to treatment failure was 57 days (95% confidence intervals: 50-58 days) with a range from 0-212 days. No patients were censored from this analysis.

Safety Analysis

Deaths

Two deaths occurred on study, were related to progressive disease, and are discussed in the Study Discontinuations section.

Number of Completed Cycles:

A completed cycle in this analysis is defined as greater than fifteen days on study in that cycle. The distribution of patients with regard to cycle completion is listed below.

Cycle	Number Completed Cycles
None.....	2
(No therapy.....)	1)
(One dose.....)	1)
One Cycle.....	3
Two Cycles.....	21*
Three Cycles.....	3
Four Cycles.....	1

Five Cycles.....	1
Six Cycles.....	2
Seven Cycles.....	1

Of the patients who completed less than two cycles of therapy, nine had objective evidence of progression and two were judged as having clinical progression.

Adherence to Dose Schedule

There were 249 protocol defined injections in this study of which 239 were given and ten (4.0%) omitted. Of these 239 injections, 184 (73.9%) were given at the assigned dose level. Twenty-one injections (8.4%) were escalated and thirty-four (13.7%) were reduced. Reasons for omission include: (1) hematemesis-two, (2) thrombocytopenia-one, (3) deep venous thrombosis-one, (4) leukocytosis-one, (4) clinical deterioration-three, and (5) social considerations-two. Reasons for dose reduction include: (1) leukopenia (with/without neutropenia) - 62.7%, (2) thrombocytopenia - 23.5%, (3) nausea - 10%, and the (4) others for unclear reasons.

Study Discontinuations

The following patients were removed from study due to adverse events as reported by the applicant::

- 001-0002 65 y/o WF with locally advanced pancreatic cancer treated at 800 mg/m². Dose 1 of cycle 2 was not given due to leukocytosis. The patient experienced grade 2 - 3 nausea and vomiting with all injections, had grade 1 diarrhea, and during in the second cycle developed a skin rash, gr. 2. The patient required hospitalization for depression. Rapid clinical deterioration occurred after the third injection of cycle two and the patient died on study due to disease. She is considered non-evaluable for response.
- 001-0010 41 y/o white male with stage IV disease, despite four doses at 1000 mg/m² over five weeks, experienced rapid clinical deterioration with evidence of objective progression at four weeks. Patient died on study due to disease with only gr. 1 nausea and vomiting reported as drug toxicities.
- 001-0007 53 y/o M with stage IV disease (hepatic mets) receive one full dose (1000 mg/m² and two reduced doses (500 mg/m²) due to grade 2 leukopenia. Patient had gr. 1 rash, gr. 1 edema, gr. 1 anemia, and one grade worsening of alkaline phosphatase (initial gr. 3), bilirubin (initial gr. 1), and AST (initial gr. 1) on therapy. He was hospitalized at the end of cycle 1 with a bleeding duodenal ulcer. New mesenteric nodes were noted on scan. Patient was removed from study and died from progressive disease two weeks later.
- 001-0013 61 y/o WF with stage IV pancreatic cancer received four cycle of therapy (1000 mg/m²) with a 50% dose reduction the third week of cycles 1-3, and the second week of cycle 4 for gr. 2 -3 nausea. The patient had flu-like syndrome reported for first cycle. Grade 2 neutropenia and grade 1 -2 SGOT elevations are reported for cycles two through four. By

the third injection of cycle four patient had developed objective evidence of progression with increase in liver size. She received other chemotherapy. Date of death unknown. Drug toxicity contributed to study discontinuation although disease progression was primary reason.

002-0028 67 y/o M with stage III disease treated with 1000 mg/m² weekly x 3 for seven cycles with dose reductions the third week of cycles 4-6 for grade 1-3 neutropenia and dose omission the third week of cycle 7. Hematuria was noted being cycle 5 while proteinuria grade 1 was noted from cycle 2 onward. Patient had grade 2 thrombocytopenia in cycle 1, grade 1 in cycle 4, grade 2 in cycle 5, grade 1 in cycle 6, and in cycle 7 grade 3 (platelets = 44,000/ul). Patient had grade 1 anemia. Patient developed mild hypertension and peripheral edema. Creatinine elevated to grade 1 (> 1.5 x normal). Patient also had flu-like syndrome and fever during study. Because these toxicities patient was removed from study. (During cycle 7 the patient developed evidence of tumor progression. With removal from study platelet count returned to normal and hematuria lessened. This clinical picture has been reported in three other patients who receive drug for > 6 cycles.

001-0009 47 y/o M with stage IV disease with markedly elevated liver function studies not appreciated (lab done > 7 days prior to study entry indicated grade 4 GGT and gr. 2 alk. PO₄ elevations) until one dose of gemcitabine had been given. Patient was hospitalized with gr. 2 fever, gr. 3 nausea and vomiting, gr. 3 chills, and moderately severe epigastric pain associated with further worsening of liver function studies (gr. 4 AST). An upper Gi bleed related to disease ensued during hospitalization. Liver function studies (AST) improved within one week after drug therapy. Patient was removed from study as ineligible. This adverse events indicates that gemcitabine therapy is contraindicated in patients with severe hepatic disease.

Adverse events not discussed by sponsor:

002-0029 This 64 y/o F with stage IV disease developed anemia with the third dose of cycle 1. She experienced grade 3 neutropenia resulting in 50% dose reduction week 2 of cycle 2. Thrombocytopenia, grade 1, was noted during week 3, cycle 2. During cycles 3, 4, 5 and 6 patient received RBC transfusions for anemia. Pt had grade 2 thrombocytopenia and grade 3 neutropenia during cycle 4. During cycle 5-6 platelet count dropped to 4,000/ul and patient received at platelet transfusion. She was also noted to have progressive disease at that time. No reports of Gi bleed. No retic counts were done. No hematuria, proteinuria or elevated creatinine was reported. Severe anemia appears to be drug related.

002-0031 49 y/o M with ? Stage IV disease refused further therapy after 14 weeks on study with gr. 1 anemia, gr.1 thrombocytopenia, and the development of grade 2-3 hematuria and proteinuria. Disease was stable at time patient left study.

Hospitalizations:

A separate section dealing with hospitalizations while on study could not be located in the study report. However a listing of serious adverse events was reported on this study and is as follows: (1) fever-3 patients, (2) nausea-3 patients, (3) vomiting-3 patients, (4) chills-2 patients, (5) rash-two patients, one requiring hospitalization, (6) flu-like syndrome- one patient with hospitalization

Treatment Emergent Signs and Symptoms

In this table only signs and symptoms related to or probably related to drug are reported. Some signs and symptoms may also be disease related. The number of patients experiencing these signs and symptoms is reported not the number of occurrences of that sign or symptom.

Table 1 : Treatment Emergent Signs and Symptoms

Sign or Symptom	Number of Patients (Total = 34)	Per Cent
Fever	10	29.4
Serious	3	
Flu-like Syndrome	7	20.6
Headache	8	23.5
Asthenia	6	17.6
Chills	6	17.6
Nausea	23	67.6
Vomiting	20	58.8
Diarrhea	3	8.8
Anorexia	2	5.8
Edema	3	8.8
Myalgia	1	2.9
Neuropathy	1	2.9
Dyspnea	4	10.8
Skin Rash	7	20.6
Proteinuria	15	44.1
Hematuria	10	29.4

One patient developed deep venous thrombosis on this study. Three serious fevers occurred: one was related to cholangitis, the other two were due to study drug.

WHO Toxicity Grading

To appreciate the degree of toxicity the worst WHO grade for each patient is presented. Grading of the

worst laboratory value for all cycles will presented first.

Table 2: WHO Grading of Laboratory Toxicities

Parameter	No. of Patient with Results	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	12	1	3	6	2	0
AST	33	12	10	7	3	1
Hemoglobin	33	11	14	1	1	0
WBC Count	33	10	8	13	2	0
Neutrophils	32	7	7	10	6	2
Platelets	33	25	3	2	2	1

Elevations of ALT and AST reported here are due to drug. Liver function elevations usually occur in cycle 1 or 2 and return to normal in subsequent cycles. Alkaline phosphatase elevation is occasionally elevated due to drug, but is usually due to the underlying disease.

With regard to myelotoxicity four patients required RBC transfusions with the transfusions in one patients secondary to a bleeding ulcer. One patient with Gr.4 thrombocytopenia required platelet transfusion for thrombocytopenia (platelet count - 4000/ul) related to drug toxicity. This patient is discussed in the Study Discontinuation section. Two other patients with thrombocytopenia, grade 3 required dose omission / reduction. One patient with grade 2 leukopenia (out of thirteen patients with grade 2 leukopenia) was discontinued from study. Two patients with grade 3 leukopenia had grade 4 neutropenia, one of whom developed febrile neutropenia. Grade 3-4 neutropenia was usually transient and reversible.

Hematuria did not occur in 66.7% of the patients in this study. In the ten patients in which hematuria grade 1 was reported for 8 patients and grade 2 in two patients. As noted in the Study Discontinuation Section one patient had creatinine elevation, grade 2 proteinuria, and hematologic abnormalities. By WHO grading only two patients had grade 1 and one patient grade 2 proteinuria.

Laboratory toxicities do not appear to be cumulative in this study. Grading of these toxicities by cycle will not be shown as the vast majority of patients were not on study for more than two cycles.

WHO Grading of Non-Laboratory Toxicities

Only those toxicities which are or may be related to drug are presented in the following table. Grading is by the worst toxicity experienced in any cycle.

Table 3: Worst WHO Grade Non-Laboratory Toxicities by Cycle

Toxicity	No. of Patients with Data	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Allergic Reaction	30	29	1	0	0	0
Rash	30	23	4	3	0	0
Fever	30	22	2	6	0	0
Infection	30	28	0	2	0	0
Mucositis	33	30	3	0	0	0
Nausea & Vomiting	30	10	6	6	8	0
Diarrhea	30	28	1	0	1	0
Neuropathy	30	29	1	0	0	0
Pulmonary	30	28	2	0	0	0

The skin toxicity usually described is a pruritic rash with occasional scaling. Rash is usually seen during the first two cycles. No patient was removed from study due to desquamation.

Fever was associated with a flu-like syndrome in six patients, with cholangitis in one (gr.2) and with neutropenia in one (gr.2). Pulmonary reactions (Three episodes occurred in two patients.) which occurred are reported as mild dyspnea. Severity of nausea and vomiting is difficult to judge due to use of antiemetics to control symptoms related to the underlying disease and for prophylaxis to prevent chemotherapy induced nausea and vomiting.

Summary

In this phase II study, thirty-three patients were enrolled, thirty-two were treated, and twenty-eight had eight or less weeks of therapy. Two partial responses of 5+ months were documented. The median time to progression was 51.5 days (range: 0 - 200) and the median time to treatment failure was 57 days (range: 0 - 212). Two deaths occurred on study due to disease. Four patients experienced significant drug related toxicity during study, while the remaining patients had grade 1-2 nausea, vomiting, leukopenia, anemia, fever and flu-like syndrome.

Appendix: E012

Table 1: E Patient Data

No.	Study No.	Stage	Date of First Treatment	Date of Progression	Date Off-Study	Response	Comments
1	001-0001	4	09-26-90		10-08-90	NE	DOS: Did not receive treatment due to worsening condition
2	001-0002	4	09-26-90	11-14-90	11-14-90	NE	DOS. No F/U CT
3	001-0003	4	11-28-90	01-23-91	01-23-91	PD	
4	001-0004	2	10-16-90	---	01-08-91	SD	Pt. refused further therapy
5	001-0005	4	01-30-91	02-27-91	02-27-91	PD	New Lung Lesion
6	001-0006	3	03-19-91	---	05-16-91	SD	Pt. refused further therapy
7	001-0007	4	08-22-91	09-23-91	09-23-91	PD	New mesenteric nodes
8	001-0008	4	09-19-91	10-17-91	10-17-91	PD	
9	001-0009	4	12-30-91	---	01-07-92	NE	Protocol . violation: Blood work > 7 days prior to entry: Had one chemo treatment
10	001-0010	4	04-16-92	05-12-92	06-02-92	PD	
11	001-0011	3	07-23-92	09-07-92	09-07-92	PD	Increase in Primary
12	001-0012	4	07-28-92	09-14-92	09-14-92	PD	Increase in Primary
13	001-0013	4	08-11-92	11-25-92	12-03-93	PD	Increase in liver mets
14	001-0014	4	10-30-92	12-17-92	01-07-93	PD	New liver mets
15	002-0021	4	03-18-91	---	04-05-91	NE	Clinical deterioration
16	002-0022	4	10-11-91	03-22-92	03-26-92	PR	PR- ----- Hepatic mets decreased by 50%; primary stable; Relapse -----
17	002-0023	3	11-22-91	---	03-26-92	PR	PR status- ----- Pt. refused further therapy after ----- with PR status
18	002-0024	4	12-16-91	02-04-92	02-04-92	PD	New hepatic lesion
19	002-0025	4	01-16-92	03-05-92	03-09-92	PD	New peritoneal disease
20	002-0026	4	01-24-92	03-13-92	03-25-92	PD	Increase in liver met
21	002-0027	4	02-06-92	02-29-92	03-26-92	PD	Increase in primary and liver
22	002-0028	3	04-06-92	10-22-92	11-03-92	SD	Gr. II hematuria and proteinuria, dyspnea, edema and pulmonary congestion; Progression in primary
23	002-0029	4	04-06-92	08-17-92	09-24-92	SD	New periaortic lymph nodes; Severe anemia requiring 6 units PRBCs during study

Appendix: E012

Table I: E012- Patient Data

No.	Study Number	Stage	Date of First Treatment	Date of Progression	Date Off-Study	Response	Comments
24	002-0030	4	05-26-92	07-16-92	07-16-92	PD	Increase liver mets
25	002-0031	4	06-11-92	---	09-02-92	SD	Pt. refusal-Hematuria, proteinuria 3+
26	002-0032	2	09-17-92	11-05-92	12-10-92	PD	New lymph node on CT
27	003-0040	3	05-15-91	06-17-91	07-10-91	SD	
28	003-0041	4	06-26-91	07-24-91	08-21-91	PD	Increase in primary and liver met
29	003-0042	2	06-26-92	-----	08-21-92	SD	Primary stable on CT; PI perception of progression
30	003-0043	3	07-04-91	-----	08-29-91	SD	Pt. refusal to continue; disease stable on scan
31	003-0044	3	01-31-92	03-06-92	03-27-92	PD	Developed livers mets, ascites
32	003-0045	4	02-14-92	04-13-92	04-24-92	PD	Increase in primary
33	003-0046	4	03-18-92	-----	05-13-92	NE	No F/U CT reported. Clinical Progression
34	003-0047	3	06-03-92	-----	07-30-92	SD	Progression noted on (off-study)

III. Review-JHAL Study Report

Title: Gemcitabine-Difluorodeoxycytidine-Phase II: Weekly x 3 Every 4 Weeks in Patients with Pancreatic Cancer

Introduction:

No case report forms were submitted for JHAL. The following review summarizes pertinent facts contained in the study report submitted by the applicant. This study, which was conducted at three centers in the US, began enrollment on January 23, 1990 and completed enrollment on November 15, 1990. The study ended February 4, 1992. Eligibility criteria, response definitions, and statistical considerations were similar to JHAL, ext and will not be reviewed here. The starting dose for this study was 800 mg/m² weekly 3 out of four weeks. If no hematologic toxicity and less than grade 1 non-hematologic toxicity was observed the dose was escalated 25% for the next cycle (1000 mg/m²), and further escalated (25%) in next cycle (1250 mg/m²) using the same toxicity parameters.

Results:

Forty-five patients were enrolled: 16 females (35.6%) and 29 males (64.4%). The median age was 63.5 years with a range of 39 to 80 years. Thirty-seven patients (82%) had stage IV disease. The performance status in the forty-four patients was 0-1, with one patient having a performance status of 2. Reasons for study discontinuations are as follows:

Adverse Event.....	5 (11.4%)
Death.....	4 (8.9%)
Lack of Efficacy, Physician Perception.....	19 (42.0%)
Lack of Efficacy, Patient and Physician Perception....	16 (35.6%)
Protocol Eligibility criteria not met.....	1 (2.2%)

To be qualified for efficacy analysis, the patient must have completed seven weeks of therapy. Forty-one patients met this criteria. One patient did not receive any therapy, and three patients did not complete the required seven weeks. The following objective tumor responses were observed:

Partial Response.....	3/45 (6.7%)
Stable Disease.....	24/45 (53.3%)
Progressive Disease.....	15/45 (33.3%)
Non-evaluable.....	3/45 (6.7%)

One patient progressed with less than seven weeks of therapy. All partial responses were confirmed by an independent Oncology Review Board. The three partial responders had stage IV disease and none had progressed by study termination. Responses lasted 3.8, 12.7, and 13 months respectively. (The clinical course of the one partial responder is described in the adverse event section.)

The median time to progression for qualified patients was 4.2 months with a range from 0.8 months to

17.1 months. The median time to treatment failure for the 41 qualified patients was 3.8 months with a range from 2.3 - 5.4 months. The median overall survival was 5.7 months (95% confidence interval: 3.8 - 17.1 months) with a range of 1.4 to 40.5+ months. (Death in one patient was not reported as of March 1, 1994.)

Safety Analysis:

Number of Completed Cycles

To have a better appreciation of the toxicity profile the number of patients completing the first six cycle is presented here:

No cycle completed.....	2 (4.4%)
One cycle completed.....	8 (17.8%)
Two cycles completed.....	7 (15.6%)
Three cycles completed.....	4 (8.9%)
Four cycles completed.....	5 (11.8%)
Five cycles completed.....	4 (8.9%)
Six cycles completed.....	5 (11.1%)
More than six cycles.....	9

Drug Exposure: Number of Injections

In this study there were 650 defined protocol injections, of which 608 were administered. Of the total defined injections 271 (41.7%) were administered at the assigned dose. Two hundred forty-one (37.1%) were escalated, ninety-six (14.8%) were reduced, and 42 (6.5%) were omitted.

Deaths and Hospitalizations

Four deaths occurred on study none of which was due to drug toxicity. Twenty-four patients were hospitalized thirty-one times. Disease related conditions account for fourteen hospitalizations, and other health related problems for five hospitalizations. Drug related toxicities accounted for twelve hospital stays including six for fever, three for nausea and vomiting, one for cellulitis, one for dehydration, and one for renal biopsy.

Adverse Events

Five adverse events were reported on study.

Patient 209-0461, a 64 y/o WM with a history of hypertension and stage IV disease, was on study for thirteen months and had a partial response at study week 16. Initial dose was 800 mg/m², escalated to 1000 mg/m² at cycle 6, 1250 mg/m² at cycle 7, and 1500 mg/m² at cycle 8 which was continued through cycle 13. Patient developed a rash starting with cycle 3 which persisted throughout treatment. Myelotoxicity was mild with grade 1-2 leukopenia and neutropenia cycles 2-13, and grade 1 nausea and

vomiting during cycles 8, 10, 11, and 12. The patient developed grade 1 anemia cycle 1 which worsened to grade 3 during cycle 13 at which time laboratory evidence of hemolysis was reported. BUN became elevated (grade 1) during cycles 8 - 12 and worsened to grade 2 during cycle 13. Creatinine was noted to be elevated during cycle 13 to 2.2 mg% and proteinuria and hematuria developed at the same time. Patient's hypertension became difficult to control. Study drug was discontinued. Renal biopsy was performed in _____ and showed an interstitial nephritis with eosinophilic infiltration and thrombotic microangiopathy considered to be drug-related. Renal function improved off study but did not return to normal. Tumor progression was noted and the patient was restarted on gemcitabine in _____ He received two doses at 800 mg/m². Two days after the second dose the patient had a myocardial infarction and died _____ from complications of the infarction. No information about laboratory data at time of retreatment is included in the patient summary.

Patient 206-0481, a 66 y/o M with stage IV disease, received two doses of gemcitabine. The first injection, 800 mg/m², was followed by gr. 3 thrombocytopenia and gr. 3 mucositis. After the second dose reduced 25% for hematologic toxicity was given on day 15, the patient developed grade 3 nausea and vomiting, grade 2 anemia requiring RBC transfusion, and grade 2 asthenia, grade 3 anorexia, and fever. Grade 2 creatinine elevation and grade 2 hematuria are attributed to bladder outlet obstruction and Klebsiella sepsis (no neutropenia reported). Despite treatment with antibiotics patient died on day _____ of study.

Patient 210-0501, a 67 y/o male with stage IV disease (hepatic and pulmonary metastases), was treated at 800 mg/m² and had a documented partial remission. During cycle 2 the patient developed a maculopapular rash which worsened despite 50% dose reduction (400 mg/m²) in cycle 3 and a further 50% dose reduction in cycle 4 (200 mg/m²) to an exfoliative dermatitis. While on therapy grade 1 nausea and vomiting, grade 2 asthenia, and grade 2 fever were noted for all cycles. The patient was discontinued from study and expired _____ from unexplained cardiopulmonary decompensation following laparotomy for a small bowel obstruction. (No evidence on lap of liver mets.)

Patient 210-0508, a 63 y/o white male with stage II disease and a history of hemochromatosis and alcohol abuse, had problems with myelosuppression (grade 2-3) necessitating continued reductions and omissions of doses during the 11 cycles on therapy. Liver function abnormalities (ALT, AST, and ALK. PO₄) of grade 1-2 were reported. When abnormalities in coagulation tests were noted during cycle 11 the patient was removed from study. It is unclear whether these are related to a paraneoplastic syndrome (considered so by investigator) or to worsening hepatic function due to alcohol abuse, hemochromatosis, and drug exposure. Patient died _____ after study discontinuation due to liver failure.

Patient 206-0504, a 52 y/o white male with stage IV disease and known hypertension, was treated with 800 mg/m² which was escalated to 1250 mg/m² by cycle six and continued on this dose to cycle 13. The patient had a partial response with disappearance of liver metastases reported at cycle 5. Toxicities included grade 2 myelosuppression, grade 1 nausea and vomiting. During cycle 11 and 12 peripheral edema developed and in cycle 13 hypertension became difficult to control. At this point the investigator decided to remove patient from study because of concerns about possible renal toxicity. On relapse 6 months later the patient was retreated with gemcitabine and experienced a second remission with no evidence of renal function abnormalities reported.

206-1026, an eighty y/o male with stage III disease was treated for seventeen cycles with little toxicity. During cycle 14 proteinuria and hematuria (grade 1) were noted. These persisted and worsened to grade 2 at cycle 18 at which point patient was removed from study with stable disease. No anemia, thrombocytopenia, or creatinine elevation is reported.

Treatment Related Signs and Symptoms

The following table summarizes the treatment related signs and symptoms which were reported during this trial. Only those symptoms which are drug-related or possibly drug related are reported here. The number of patients who report a sign or symptom at least once are reported. No information about the frequency and little information about severity of symptoms is available with this reporting system.

Table 1: Treatment Related Signs and Symptoms

Sign/Symptom	No. of Patients	No. with TESS	Per Cent (%)
Asthenia	45	33	73.3
Anorexia	45	19	42.2
Nausea	45	27	60.0
Vomiting	45	25	55.6
Diarrhea	45	14	31.1
Mucositis	45	2	4.4
Flu Syndrome	45	7	15.6
Fever Serious	45	24 4	53.3
Chills	45	17	37.8
Myalgia	45	24	53.3
Headache	45	18	40.0
Malaise	45	7	15.6
Rash	45	13	28.9
Urticaria	45	1	2.2
Alopecia	45	11	24.4
Edema Peripheral	45	10 11	22.2 33.3
Injection Site Reaction	45	1	2.2
Dyspnea	45	8	17.8

Two of the four serious fevers were due to cholangitis.

WHO Toxicity Grading

To better appreciate the toxicity profile of the drug in this study the WHO toxicity for hematological and non-hematological toxicity is presented in the following table. The most severe grade in all cycles for each patient is presented in this table.

Table 2: WHO Toxicity Grading - Laboratory Parameters

Laboratory Value	No. Patients with Data	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	14	5	5	4	0	0
AST	44	6	18	8	9	0
BUN	44	34	8	2	0	0
Creatinine	43	36	5	2	0	0
Hemoglobin	44	13	15	12	4	0
Leukocytes	44	20	15	6	3	0
Neutrophils	44	22	4	10	5	3
Platelets	44	30	9	1	4	0

In this study six patients had RBC transfusions and one of these patients also required platelet transfusion for thrombocytopenia. Two patients had three instances of deep venous thrombosis. Hematuria of grade 1 or 2 was reported in 47.7% of patients, proteinuria of grade 1 -2 in 31% of patients.

Table 3: WHO Grading - Non-Hematologic Toxicities

Toxicity	No. Patients with Data	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous	44	24	16	3	1	0
Alopecia	44	33	11	0	0	0
Fever	44	18	11	14	1	0
Infection	44	38	5	0	1	0
Allergic	44	43	1	0	0	0
Pulmonary	44	34	2	7	0	1
Mucositis	45	37	5	1	1	0
Nausea & Vomiting	45	4	18	16	4	2
Diarrhea	45	25	13	4	2	0
Peripheral Neurotoxicity	45	36	8	0	0	0

With regard to cutaneous toxicity, one patient (discussed in the Adverse Event section) developed an

exfoliative dermatitis. Three patients with grade 2 rash are reported to have erythematous maculopapular eruptions with desquamation. Alopecia was minimal. The one patient with grade 3 infection had Klebsiella sepsis (discussed in the Adverse Events section). The patient with grade 4 dyspnea had multiple pulmonary emboli and died on study. Nine other patients with grade 1-2 pulmonary toxicity had grade 1-2 dyspnea, but no bronchospasm. One patient developed oral ulcers on study (grade 3 mucositis) requiring a liquid diet and is reported in the Adverse Events section. The neurotoxicity reported in this study consists of paresthesias and decreased reflexes. As in all studies, somnolence is noted in the study report. It is not reported here since it is impossible to determine how much, if any, is due to study drug, how much is due to analgesic or antiemetic therapy, and how much is due to compromised organ function secondary to disease.

Summary

In this phase II study forty-four patients were enrolled and three patients (6.7%) were reported to have partial responses. Five adverse events were reported including three in the partial response patients. The median survival for qualified patients (41) was 5.7 months, the median time to progression for qualified patients (41) was 4.2 months and the median time to treatment failure for qualified patients (41) was 3.8 months. Non-laboratory toxicities include: asthenia - 73%, nausea and vomiting - 55%, fever - 53%, myalgia - 53.3%, peripheral edema - 33.3%, edema -22.2%, and rash - 28.9%. Myelosuppression included reports of anemia in 70% of patients with grade 3 in 9%, leukopenia in 54.5% with grade 3 in 6.8%, thrombocytopenia in 31.8% with grade 3 or greater in 9.1%.

Appendix: JHAL

Adverse Events Listing -JHAL

No.	Study No.	St.	Treatment	Progression	Death	Response	Comments
1	206-481	4	06-08-90	---	-----	NE	Off-Study: 06-30-90, Hospitalized with Klebsiella sepsis, renal failure
2	209-1026	4	09-04-90	---	-----	SD	Proteinuria, hematuria, decreased haptoglobin
3	209-1030	4	09-11-90	---	-----	SD	DOS: ruptured aortic aneurysm
4	209-1032	2	10-16-90	---	-----	NE	DOS: CA
6	209-461	4	01-23-90	---	-----	SD	Had response almost PR; No treatment after ----- when pt. developed renal disease due to drug
7	209-473	4	05-22-90	07-11-90	-----	PD	Increase in disease ----- PTE on ----- died from PTE and disease -----
8	210-501	4	04-09-90	---	-----	SD	DOS: cardiac arrest
9	210-504	4	08-22-90	10-16-90	-----	-----	AE: Developed umbilical nodule ----- later reported to present since study entry; Pleural mass new ----- not biopsied; Considered PR by investigator due to complete disappearance of liver mets with shrinkage of pancreatic mass; Off study due to new hypertension and PI concern about possible renal toxicity
53	210-508	2	12-05-90	---	-----	SD	Developed coagulopathy with liver failure, reported to abuse alcohol, dose of drug reduce by 90% with many missed treatments due to low blood counts; death due to liver failure, ? etiology

VIII: SAFETY REVIEW-GEMCITABINE

From March 1, 1994 to September 8, 1994 a total of 1825 patients were entered into 45 trials using gemcitabine as a single agent . Of this group 979 patients were enrolled in trials using weekly dosing schedules with doses ranging from 800 - 1250 mg/m² . Of the 979 patients, 244 (13.4%) has pancreatic cancer and were treated in the five studies reviewed in detail earlier in this NDA review. This group of 979 patients is considered as the primary subset of patients for the detailed safety analysis. Of the remaining 846 (46.4%) patients, 511 were treated using different dosing schedules / dose ranges. Another 335 patients were treated on the same dosing schedule / dose level but the safety data was not reported electronically, therefore the data from these patients was not included in the electronic safety data base. Summaries of the safety data from each of these trials are included in the NDA. For the 979 patients included in the data base the median number of cycles received was two (eight weeks to twelve weeks) and the mean was 3.1 cycles (? days since cycle length is variable). No information about the minimum, maximal, or average dose in mg/m² is included in the safety data base.

Patient Demographics:

Integrated safety summary for the 979 patients treated with a weekly schedule of gemcitabine includes a listing of all serious adverse, unexpected, or possibly causally related adverse events (AEs), study discontinuations due to adverse events, and a summary of treatment emergent signs and symptoms (TESS) for chemo-naïve patients vs previously treated patients, by sex (male vs. female), and by age (< 65 years, ≥ 65 years). No analysis by race is possible since the Caucasian race was reported by over 90% of the study population and for 278 (28.3%) patients race was not reported. Of the 979 patients in the integrated safety summary (ISS), 783 (80%) are chemo-naïve and 196 (20%) had been exposed to other chemotherapy agents. All patients in this data base received at least one dose of gemcitabine. Since the length of the first cycle was variable (from three to eight weeks) any patient who was enrolled for 15 days of a cycle is counted as having completed the cycle. Table 1-SR presents the characteristics of the study population.

Deaths:

In the 979 patient ISS data base 45 (4.6%) patients died on study . The cause of death for 697 patients who died after removal from study but prior to March 1, 1994 were also evaluated for possible relationship to study drug. In ninety-seven patients the cause of death had not been evaluated by the applicant at the time that the NDA was filed.

Of the forty-five patients who died on study, five deaths can be considered gemcitabine-related and are discussed here.

E012-001-001 60 y/o M with IIIB NSCLC had cardiac arrest after receiving second gemcitabine infusion of Cycle 7. Had developed atrial fibrillation while on gemcitabine.

Table 1-SR: Demographics of Patients in the ISS Study Base

Parameter	ISS Data Base (N = 979)	Pancreatic Patient Group (N = 244)
Sex		
Female	399 (40.8)	101 (41.4)
Male	580 (59.2)	143 (58.6)
Origin		
African Descent	40 (5.7)	4 (1.9)
Caucasian	602 (85.9)	193 (91.5)
Asian	15 (2.1)	2 (0.9)
Hispanic	23 (3.3)	12 (5.7)
Other	21 (3.0)	—
Unspecified	278	33
Age (No. of Patients)	N = 976	N = 244
Median	60.0 yrs.	62.00
(Range)	(23.0 - 84.0 yrs.)	(33.0 - 82.0 yrs.)
Height (No. of Patients)	N = 979	N = 244
Median	168.9 cm.	169.5 cm.
(Range)	(135 - 197.0 cm.)	(145 -193 cm.)
Weight (No. of Patients)	N = 978	N = 244
Median	68.4 kg	68.1 kg
Range	(31.1 - 124.2 kg.)	(35.8 - 108.6 kg)
Hx. of Smoking	194 (27.7)	55 (26.2)
Hx. of Alcohol Use	269 (38.4)	67 (31.8)
Use of Caffeinated Beverage	545 (78.0)	161 (76.3)
Chronic Illness		
No. without Chronic Illness	231 (23.6)	16 (6.6)
No. with ≥ 1 Chronic Illness	748 (76.4)	228 (93.4)
Hypertension	193 (19.7)	64 (26.2)
Arthritis	89 (9.1)	19 (7.8)
Diabetes Mellitus	79 (8.1)	40 (16.4)
Lung Disorder	59 (6.0)	15 (6.1)
Cardiovascular Disease	55 (5.6)	25 (10.2)
Concomitant Medications		
No. with No Drugs	42 (4.3)	1 (0.4)
No. with ≥ 1 Drug	937 (95.7)	243 (99.6)
Paracetamol	420 (42.9)	139 (58.6)
Metoclopramide*	290 (29.6)	74 (33.3)
Morphine*	328 (32.8)	168 (68.8)
Prochlorperazine*	232 (33.9)	126 (51.6)
Furosemide	142 (14.5)	39 (16.0)
Lorazepam	157 (16.0)	55 (22.5)
ASA	112 (11.4)	19 (7.8)
Dexamethasone	100 (10.2)	19 (7.8)

E007-005-0033

63 y/o F with Stage IV epithelial ovarian cancer who developed pancytopenia

while on gemcitabine and died from a heparin related bleed despite intensive hematological support.

- JHAO-227-0791 63 y/o F with extensive SCLC developed severe bronchospasm after a second dose of gemcitabine partially relieved with salbutamol and died within _____ hours from respiratory insufficiency.
- E010-001-0022 74 y/o Hypernephroma patient developed interstitial pneumonia following two doses gemcitabine; _____ with no response to antibiotics. (?Drug-induced interstitial pneumonitis)
- 018-601-0244 50 y/o M Stage IV poorly differentiated squamous cell carcinoma of the lung developed dyspnea three days post gemcitabine treatment with chest x-ray showing no change. (? Drug-induced interstitial pneumonitis)

The majority of the 697 deaths which occurred after discontinuation from study were due to disease progression. Five deaths in the off study group are reviewed in more detail in the NDA since prior treatment with gemcitabine may be, in part, responsible for the patient's demise. In two cases of hepatic failure (E018-802-0267, JHAL-210-0508) gemcitabine played a role in the decrease in liver function. In the third case of liver failure (JHAY-271-3297) disease progression appears to be the culprit. One death due to renal failure (E012-003-0045) is attributed to septic shock associated with non-neutropenic sepsis. The fifth mortality described in the review is an ovarian cancer patient previously treated with alkylators and etoposide who developed leukemia after six cycles of therapy. This leukemia is most likely secondary to previous chemotherapy.

Study Discontinuations Due to Adverse Events

One hundred two (10.4%) patients in the ISS data base (979 patients) were discontinued from study due to adverse events. Detailed reports for each study discontinuation is found in the study report for that trial. For the 244 pancreatic patients the pertinent adverse reactions are reviewed in the respective study sections of this NDA. Due to the type of summary listings from the Event Classification titles it is sometimes difficult to discern whether an adverse event is disease or drug related. Table 2-SR below regroups those adverse event classifications thought to be drug related into body systems classifications in order to appreciate better the magnitude of those adverse events which are likely related to drug.

Brief summaries of the clinical course of those patients who discontinued study due to dyspnea (6), hepatic failure (1), abnormal liver function studies (4), and renal failure (2), and coma (1) were presented in the NDA and are briefly listed here. In four of six cases in which dyspnea was the reason for study discontinuation the adverse event is clearly related to study drug administration. In the four case of liver failure exposure to gemcitabine was partially responsible for worsening hepatic function. In two of six patients removed from study due to worsening LFTs the combination of alcohol and gemcitabine resulted in hepatic toxicity. In two other patients removed from study due to abnormal liver function studies drug exposure appeared to be the only factor which accounted for the hepatic dysfunction. One of two patients

Table 2-SR : Study Discontinuations - Adverse Event Classification

Event Classification	No. of Patients Discontinued
Systemic	
Asthenia	11
Flu Syndrome	1
Myalgia	1
Cachexia	1
Malaise	2
Somnolence	2
Fever	3
Pulmonary	
Dyspnea	6
Asthma	1
Pneumonia	2
Hepatic	
Abnormal LFTs	4
Hepatic Failure	1
Cardiac	
Arrhythmia	2
Hypertension	2
Myocardial Infarction	4
Lung Edema	2
Congestive Heart Failure	1
Left Heart Failure	1
Abnormal EKG	1
Hypotension	1
Gastrointestinal	
Nausea and Vomiting	4
Nausea	3
Vomiting	2
Gastrointestinal Hemorrhage	2
Hematemesis	1
Ascites	1
Peripheral Edema	4
Edema	2
Hematologic Abnormalities	
Thrombocytopenia	4
Anemia	2
Leukopenia	1
Renal Failure	3
Abnormal Renal Function	2
Hematuria	1
Albuminuria	1
Mucositis	1
Allergic Reactions	
Rash	1
Maculopapular Rash	1
Urticaria	
Other	
Cerebrovascular Accidents	3
Cerebral Ischemia	1
Cellulitis	1
Sepsis	2
Abdominal Pain	1
Abscess	1
Coma	1
Deep Venous Thrombosis	1
Chest pain	2
Pain	1
Depression	2

removed from study due to renal failure had hemolytic-uremic syndrome and required dialysis on a permanent basis after recovery from the hemolytic-uremic syndrome. In the other patient removed from study due to renal failure, gemcitabine treatment had no relationship to the development of renal failure. For each of the pancreatic cancer trials, study discontinuations for adverse events were reviewed in the study summaries. In the pivotal trial (JHAY) and the supporting trial (JHAZ) case report form review yielded additional adverse events not reported by the applicant and responsible for the patient's discontinuation from the clinical trial. In reviewing the above table, sixty-five (63.7%) discontinuations can be attributed to drug toxicity. For the entire ISS data base about 6.6% of the patients went off study due to drug related adverse events.

Treatment Related Serious Adverse Events

Treatment-emergent signs and symptoms (TESS) are defined as any change in the clinical status of the patient, irrespective of causality. Worsening of signs / symptoms or new signs / symptoms are reported in this database. In the gemcitabine trials 964 (98.5%) of the 979 patients in the ISS database reported one or more TESS. Three hundred fifty-six TESS events were judged by the COSTART term classification to be serious adverse events. Note that causality or worsening of a symptom could be due to study drug, underlying disease, or intercurrent illness. Table 3-SR presents information on the number of cycles of gemcitabine therapy which were administered to chemo-naive and previously treated patients in the ISS database. (These patients were treated on the same dosing schedule with doses ranging from 800 - 1250 mg/m² so that a drug exposure could vary by over twofold, from a minimum of 1600 mg/m² to a maximum of 3750 mg/m² per cycle).

Table 3-SR : Demographics of Patients with Serious Adverse Reactions

Parameter	Chemo-naive	Previously Treated
No. of Patients	783	196
Male / Female	580 / 399	
< 65yrs. / ≥ 65 yrs.	651 / 328	
Mean No. of Cycles	3.6	3
Median No. of Cycles (Range)	3.0 (0-38)	2.0 (0-19)

Twenty-six percent of the chemo-naive patients and 25.5% of the previously treated patients received two cycles of therapy (about eight weeks). Since most protocols specified disease reevaluation at eight weeks, a large number of patients went off-study at eight weeks. Serious adverse reactions were experienced by 285 (36.4%) chemo-naive patient and 71 (36.2%) of the previously treated patients. For each group those adverse reactions which occurred more than 1% of the time and were judged by the reviewer to be related to study drug are listed in the following table (Table 4-SR).

Table 4-SR : Incidence of Serious Adverse Events in Chemonaive and Pretreated Patients

Parameter	Chemonaive (N=783)	Previously Treated (N=196)
Dyspnea	41 (5.2%)	7 (3.6%)
Fever	39 (5.0%)	12 (6.1%)
Anemia	37 (4.7%)	12 (6.1%)
Vomiting	36 (4.6%)	14 (7.1%)
Nausea	31 (4.0%)	13 (6.6%)
Dehydration	16 (2.0%)	6 (3.1%)
Peripheral Edema	14 (1.8%)	3 (1.5%)
Edema	10 (1.3%)	1 (0.5%)
Thrombocytopenia	9 (1.3%)	2 (1.0%)
Asthenia	12 (1.5%)	7 (3.6%)
Flu Syndrome	7 (0.9%)	2 (1.0%)

Eighty-seven patients (11.1%) of the chemonaive and fifteen (7.7%) of the previously treated patients were discontinued due to adverse events. More episodes of dyspnea was encountered in the chemonaive patients, while anemia, nausea, and vomiting were more common in the previously treated patients. No significant difference in the number and type of adverse events between groups was noted. With regard to fever fifty-one patients reported episodes of serious fever, in seven sepsis was associated with the fever and six of the seven had leukopenic sepsis with fever.

In four of 979 patients hemolytic-uremic syndrome has been suspected or documented and in two other patients histopathologic examination of renal tissue revealed changes consistent with HUS. In the TESS review by Body System twelve (1.2%) cases of "erythrocytes abnormal" are noted and one case of hemolytic anemia is reported. The sponsor has cautioned in the labelling that HUS may develop in patients with impaired renal function treated with gemcitabine.

Over ninety-eight per cent of the patients enrolled in this database had some treatment related signs and symptoms as noted above. The following table lists the most frequent sign/symptoms which could be related to study drug exposure selected from the line listings classified by body system.

The TESS listing found in the "Cardiovascular" area are not reported since none of the events classifications appeared related to study drug toxicity. Myocardial infarction, congestive heart failure, pericardial effusion, and arrhythmia are reported with about equal frequency in both the ISS group and the pancreatic group. In JHAY a greater number of patients experienced venous thrombosis, most likely related to the underlying disease state. In the "Body as a Whole" category the most frequently occurring signs and symptoms are those related to the "Flu-like Syndrome" and include fever, chills, malaise, and asthenia. Myalgia ("Musculoskeletal System") can also be included as part of this constellation. The number of patients (21/979) who discontinued study due to this constellation of drug related symptoms is a small compared to the number of patients (> 50%) who report these adverse side effects. Fever was reported at least once in 44% of patients, peripheral edema (edema) in over 33%, nausea in 65%, vomiting in 43% of patients, anorexia in 27%, constipation in 22%, diarrhea in 20%, rash in 24%, and dyspnea in 26% with serious dyspnea in 5%. Albuminuria (41.5%), hematuria (18.6%), anemia (22%), leukopenia (32%), thrombocytopenia (17%), increased SGOT (13%) and increased SGPT (9%). Serious adverse

reactions which occur in 1% or less of cases include hemolytic-uremic syndrome and drug related pulmonary parenchymal changes (pneumonitis). In patients with preexisting hepatic disease hepatic failure which appears to be drug related had been reported. No studies have been done in patients with impaired hepatic function. In terms of WHO grading of non-laboratory toxicities grade III/IV nausea and vomiting were reported in 105/561 (18.3%) patients. Any other grade III/IV toxicity related to drug was reported in less than 1% of the patients.

Table 5-SR : Most Frequent Drug Related TESS by Body System

TESS by Body System	No. of Patients (%) (N ≤ 979)
Body as a Whole	851 (86.9)
Fever	432 (44.1)
Asthenia	410 (42.0)
Flu Syndrome	185 (18.9)
Chills	156 (15.9)
Malaise	58 (5.9)
Allergic Reaction	11 (1.1)
Injection Site Pain, Reaction, Inflammation. Hemorrhage, Hypersensitivity	44 (4.5)
Cardiovascular	281 (28.7)
Gastrointestinal	823 (84.1)
Nausea	633 (64.8)
Vomiting	421 (43.1)
Anorexia	266 (27.3)
Constipation	214 (22.0)
Diarrhea	193 (19.8)
Dyspepsia	53 (5.4)
Flatulence	52 (5.3)
Abnormal Liver Function Studies	45 (4.6)
Stomatitis	42 (4.3)
Endocrine	9 (0.9)
Hemic and Lymphatic System	552 (56.4)
Leukopenia	315 (32.2)
Anemia	215 (22.0)
Thrombocytopenia	166 (17.0)
Metabolic / Nutritional Systems	410 (52.1)
Peripheral Edema	199 (20.3)
Edema	130 (13.3)
Generalized Edema	4 (0.4)
SGOT Increased	103 (13.3)
SGPT Increased	91 (9.3)
Musculoskeletal	200 (20.4)
Myalgia	130 (13.3)
Nervous System	417 (42.6)
Somnolence	135 (13.8)
Insomnia	103 (10.5)
Dizziness	89 (9.1)
Depression	80 (8.2)
Anxiety	68 (7.0)
Paresthesia	58 (5.9)
Confusion	42 (4.3)
Nervousness	30 (3.1)
Hypesthesia	15 (1.5)
Neuropathy	15 (1.5)

Table 5-SR: Most Frequent Drug Related TESS by Body System

Respiratory System	
Dyspnea	250 (25.5)
Increased Cough	177 (18.2)
Rhinitis	81 (8.3)
Pneumonia	26 (2.7)
Lung Disorder	25 (2.6)
Skin and Appendages	420 (42.9)
Rash	209 (21.3)
Maculopapular Rash	24 (3.5)
Alopecia	134 (13.8)
Pruritus	85 (8.7)
Special Senses	122 (12.5)
Taste Perversion	44 (4.5)
Amblyopia	15 (1.5)
Urogenital System	405 (41.4)
Albuminuria	205 (20.9)
Hematuria	182 (18.6)
Abnormal Kidney Function	8 (0.8)
Kidney Failure	4 (0.4)

Treatment Related Changes in Clinical Laboratory Evaluations

Analysis of the laboratory data for the entire group of 979 patients as well as for the 242 patients enrolled in the pancreatic cancer studies is included in the safety analysis. Laboratory tests evaluating the hematopoietic system, hepatic function, and renal function were analyzed. For purposes of analysis the laboratory tests were divided into two groups. For Group I lab tests (AST, ALT, alkaline phosphatase, GGT, LDH, total bilirubin, BUN and creatinine) the tests were compared to the upper range limit of their respective laboratory's reference range for evaluation. The upper limit of the range was normalized to 100% for data analysis purposes. For group II (Hgb, Hct., WBC, differential counts, platelets, U/A, uric acid, total protein, albumin, calcium, uric acid, phosphorus) the values were converted to the same reporting units and a Common Acceptable Reference Range (CARR) was developed to analyze the lab results. In order to detect changes in central tendency for each analyte the following were analyzed: average differences between the endpoints and the baseline measurements, the minimum and baseline measurements, between the maximum and baseline measurements using the baseline and follow-up results available for the specific analyte. The Wilcoxon signed-rank test was used in each case to test for the null hypothesis of no treatment effect (no change from baseline). With the use of modified box whisker plots analyses of trends of extreme analyte values by time on study and study drug exposure were performed for selected analytes from the ISS database population and from the pancreatic cancer subset.

In evaluating the hematology data a statistically significant change from baseline to endpoint was noted in the following laboratory values: Hgb (mean fall of 1.2 gm%), hematocrit, RBC mass, WBC count, lymphocytes, monocytes, eosinophils, and basophils. The platelet count increase (about 65% from baseline to endpoint) was statistically significant and consistent with reactive thrombocytosis observed from cycle 3 onward. As expected the change from baseline to minimum and maximum value was statistically significant for all hematological parameters. Box whisker plots by cycle show a gradual decrease in hemoglobin and RBC count over time (follow-up over 10 cycles), while for the total WBC, neutrophils and other leukocyte populations, and platelets an initial drop is seen with the first cycle and stabilized in subsequent cycles. Examination of box whisker plots by cumulative study drug dose shows a mild decrease in erythrocyte counts, hematocrit values, and WBC with increasing total dose. Platelet counts did not change with increasing total dose up to 12,000 mg/m² (about four months of treatment).

With regard to renal function a statistically significant increase in urinary pH from baseline during treatment was noted along with a tendency for increased BUN. Creatinine, calcium, phosphorus, and anion gap had statistically significant minimums as compared to baseline but were not considered clinically significant. Box whisker plots confirm a rise in urine pH from baseline value and an increase in the BUN to the upper limit of normal. Box whisker plots indicate a decrease in anion gap, calcium, and phosphorus concentrations from baseline over time which is not clinically significant and probably reflects decreases in serum proteins due to the underlying disease process.

Laboratory tests which reflect hepatocellular and biliary function are positively statistically significantly elevated (baseline to maximal value) with gemcitabine therapy and include AST, ALT, alkaline phosphatase, and bilirubin. Two-thirds of patients had elevation of at least one liver function study with grade III/IV elevation seen 9 - 10%. Study discontinuation due to liver function abnormalities occurred in about 0.5%. Total protein and albumin are statistically significantly decreased (baseline to minimal value) probably due to the underlying disease state or possibly due to drug related decreased hepatic synthesis. Box whisker plots show that the distribution of maximal values is 4- 25 times the upper reference limit for AST in cycle 1 and decreases in the following cycles. ALT follows a similar pattern although not as pronounced as for AST. Box whisker plots by cumulative drug dose shows that ALT/AST elevation occurs at all doses levels from < 3000 mg to > 12000 mg. With regard to maximal and minimal changes for liver function studies (ALT, AST, and alkaline phosphatase) from baseline value, change is difficult to appreciate with the graft used since the y-axis is divided by 200 percentage point increments from zero to 3-7000%. The maximal values for each LFT tends toward the upper limit of normal over a ten cycle follow-up for the treated group.

In evaluating the laboratory data using WHO criteria the following table provides information about the incidence of grade III/VI laboratory toxicity for the 979 patients included in the safety analysis.

Table 6-SR: Number (%) of Patients Experiencing WHO Grade III/IV Laboratory Toxicity

Laboratory Test	No. of Patients with Lab Value	No. of Patients with Gr. III/IV Toxicity (%)
Alkaline Phosphatase	959	81 (8.4)
Alanine Transaminase	772	74 (9.6)
Aspartate Transaminase	919	78 (8.9)
Bilirubin	956	25 (2.6)
BUN	904	0
Creatinine	961	1 (0.1)
Hemoglobin	967	79 (8.2)
White Blood Count	967	90 (9.3)
Segmented Neutrophils	947	241 (25.4)
Platelets	967	51 (5.3)

In conclusion, decreases in hemoglobin, hematocrit and erythrocyte counts were seen over time with gemcitabine treatment. White blood counts decreased during the first cycle but then stabilized. No cumulative white cell toxicity either in terms of increasing nadirs or progressive decrease in total white count was seen, nor was any cumulative platelet toxicity observed. While a rise in urine pH is seen, no anion gap was detected with continued treatment. BUN rises to the upper limit of normal, but not increase in creatinine was seen. Liver functions were elevated above the upper limit of normal with treatment in

many patients but no cumulative effect was seen and maximal values tend to revert to normal over time. No difference was detected between the pancreatic cancer subgroup and the entire group in terms of laboratory values.

Gemcitabine Safety in the Elderly

Table VI contrasts the difference in adverse effects by age. In the integrated Safety Analysis a special subsection is devoted to the elderly since this drug has reduced clearance in the elderly (and in women). The amount (median, mean, range) of drug in mg/m² which each age group received can not be determined from the analysis so that, while the safety profiles appears similar in both age groups, the profiles may be based on different levels of drug exposure. With regard to the WHO grading no differences were observed in the number of Grade III/IV toxicities between the patient population less than age 65 and greater than age 65.

Table 7-SR: Comparison of Adverse Effects by Age

Parameter	< Age 65	≥ Age 65
No. of Patients (%)	651 (66.5)	328 (33.5)
Cycles of Therapy		
Median	3.0	3.0
Mean	3.5	3.4
Maximum	38	18
Most Common Number	2	2
No. of Serious Adverse Events (%)	240 (36.9)	116 (35.4)
Most Frequent Serious AEs		
Anemia	37 (5.7)	12 (3.7)
Vomiting	36 (5.6)	14 (4.3)
Dyspnea	33 (5.1)	15 (4.6)
Fever	33 (5.1)	18 (5.5)
Nausea	33 (5.1)	11 (3.4)
Asthenia	14 (2.2)	5 (1.5)
Dehydration	13 (2.0)	9 (2.7)
Edema, Peripheral Edema	19 (2.9)	9 (2.7)
Study Discontinuations	68 (10.4)	34 (10.4)
Most Common Reasons		
Asthenia	6 (0.9)	5 (1.5)
Nausea and Vomiting	4 (0.6)	2 (0.6)
Fever	3 (0.5)	-
Abnormal LFTs	3 (0.5)	2 (0.6)
Edema	3 (0.5)	2 (0.6)
Dyspnea	2 (0.3)	4 (1.2)
Common Treatment Emergent Signs and Symptoms	No. of Patients (%)	No. of Patients (%)
Nausea	440 (67.8)	193 (59.0)
Vomiting	305 (47.0)	116 (35.5)
Fever	289 (44.4)	143 (43.6)
Asthenia	269 (44.4)	141 (43.0)
Leukopenia	222 (34.1)	93 (28.4)
Anorexia	163 (25.0)	103 (31.7)
Dyspnea	163 (25.0)	87 (26.5)
Anemia	149 (23.0)	66 (20.1)
Albuminuria	148 (22.7)	57 (17.4)
Rash	144 (22.1)	65 (19.8)
Headache	135 (20.8)	56 (17.2)
Hematuria	131 (20.1)	51 (15.5)
Flu Syndrome	130 (20.0)	55 (16.9)
Diarrhea	114 (17.5)	79 (24.2)
Peripheral Edema, Edema	200 (30.7)	129 (39.3)
Thrombocytopenia	99 (15.2)	67 (20.4)

Pulmonary Toxicity

Seven patient were observed to have interstitial pneumonia, pulmonary fibrosis, or nodular infiltrates considered secondary to drug therapy. Fifteen patients had dyspnea within twenty-four hours of gemcitabine therapy with no other explanation for the dyspnea. Nine patients who were noted to have dyspnea within twenty-four hours of gemcitabine administration had the dyspnea ascribed to disease progression in the absence of pleural effusion, pericardial effusion, or previous history of dyspnea due to pulmonary disease.

Renal Toxicity

Forty-two patients (1.7%) from a total population of 2,429 patients are considered by the applicant to have drug related disease. The following table (Table 8-SR) categorizes the type of renal related dysfunction associated with gemcitabine or the gemcitabine combinations where N is the number of patients at risk.

Table 8-SR: Renal Abnormalities Associated with Gemcitabine Containing Regimens

Type of Abnormality (N = 2429)	Number of Reports / Chemotherapy Regimen			
	Gemcitabine Alone (N = 2096)	Gemcitabine +Vindesine (N = 42)	Gemcitabine + Cisplatin (N = 36)	Gemcitabine + Carboplatin (N = 3)
Abnormal Renal Function	5	3	5	0
Renal Failure	20	1	0	0
Acute Renal Failure	4	0	2	0
Uremia	3	0	2	1
Hemolytic Anemia	4	0	0	0

For seven patients more than one type of renal abnormality is reported. In the four cases of renal dysfunction / renal failure associated with vindesine microscopic and/ or gross hematuria was involved and death due to drug related renal failure occurred in one patient. Hemolytic-uremic syndrome could not be confirmed. Five cases of HUS or suspected HUS occurred in patients treated with gemcitabine alone. One patient treated with gemcitabine and carboplatin developed hemolysis and renal failure and died from renal failure. For the seven patients who developed renal abnormalities on a gemcitabine-cisplatin combination, cisplatin was judged to be the responsible agent in all cases.

SUMMARY:

Over two thousand patients have had exposure to gemcitabine alone or in combination with other agents utilizing a variety of dosing schedules. Information about the safety of the weekly dosing schedule with doses ranging from 800 - 1250 mg/m² for gemcitabine is available from a 979 patient database. Five drug related deaths occurred which, in the reviewer's judgement, were definitely related to gemcitabine treatment: three related to pulmonary toxicity, one due to neutropenic sepsis, and one due to cardiac arrest while receiving drug. One hundred two patients in the 979 patient data base discontinued treatment

due to adverse events either related to disease or to therapy. In fourteen cases drug related adverse events could definitely be documented to be the reason for study discontinuation. About thirty per cent of the patients reported at least one treatment related serious adverse event. Adverse events associated with gemcitabine include nausea (65%), vomiting (43%), diarrhea (19%), edema (~ 33%), rash (21%), dyspnea (25%), and "flu-like syndrome" (19%) which may be manifested by any of the following: fever (44%), chills (19%), myalgias (13%), malaise (16%). The principal laboratory toxicity is myelosuppression (56%) with leukopenia, neutropenia, anemia, and less frequently thrombocytopenia. Myelosuppression is usually grade I/II and is readily reversible. Other significant laboratory abnormalities include elevated liver function studies (4.6%) including SGOT and SGPT and urinary abnormalities (39%) including hematuria and proteinuria.

Comparison of toxicities by age did not show a difference in distribution of toxicities in the population over age sixty-five and those less than sixty-five. No information is included about the total cumulative dose in each age group or the cumulative dose per cycle by age group. No definitive statement about safety in the elderly can be made until this information is provided. Likewise no information about total cumulative dose and the cumulative dose per cycle is provided so that definition of a dose - toxicity curve is difficult. Only anecdotal information is available about the safety of gemcitabine in patients with impaired renal or hepatic function. From a few reports impaired hepatic function appears to greatly enhance toxicity. Hemolytic-uremic syndrome has been documented with this drug and the sponsor advises that "gemcitabine should be used with caution in patients with impaired renal function. It should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin or LDH...". Based on the information provided in the NDA the safety profile of this drug is acceptable.

[Redacted content]

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X § 552(b)(4) Draft Labeling

APR 26 1996

MEDICAL OFFICER REVIEW: NDA 20509, AMENDMENT B2

NDA: 20509
AMENDMENT: B2
SUBM. DATE: March 13, 1996
DRUG: Gemcitabine (Gemzar^R)
APPLICANT: Eli Lilly and Company
Indianapolis, Indiana
REVIEWER: G.A. Schechter, M.D.
DATE: April 18, 1996
REVISED: April 26, 1996

In response to Comments and Deficiencies from the Clinical and Pharmacology /Toxicology and the Clinical Comments on the Four Month Safety Update the applicant, Eli Lilly, submitted a two volume amendment which addresses the labelling and safety issues. The applicant's responses to the Clinical Deficiency Comment section from the NDA and the Clinical Comments from the Four Month Safety Update Review are presented in this document. The original comments transmitted to Eli Lilly (*Comment #-*), review of the applicant's responses to each of the comments (*Applicant's Response*), and the clinical reviewer's response (*FDA Response*) are included in this document.

I. NDA SAFETY DATA :

Comment #1: In the Overall Safety Review Section, information about drug toxicity is reported by number of cycles but not by dose range/cycle. The median total dose (in mg/m^2) and the range of total dose as well as the median dose (mg/m^2) per cycle and range of dose per cycle (in mg/m^2) for each cycle, the number of patients at risk, and the drug-related toxicity grading and treatment emergent signs and symptoms for these different dose ranges should be correlated. Since the clearance of this drug is reduced in the elderly and in women, the number of treatments/cycle is variable, and dosage reductions occurred in many patients a dose/toxicity correlation is needed to accurately define Gemcitabine's toxicity profile.

Additional information must be provided to show that a dose of $1000 \text{ mg}/\text{m}^2$ weekly three out of four weeks is safe in the elderly, especially in elderly women, since the clearance of drug is markedly reduced in this population. Please provide more information on the number of elderly men and woman exposed to drug, the total dose to which each patient was exposed, the dosing schedule on which the patient was treated, the toxicities observed by total dose, and information on dose reductions due to toxicity in subsequent cycles of therapy in this age group.

Review of the Safety Data:

Review of the Safety Data:

The safety data was divided into four attachments.

Attachment I Part I:

Description: In the Tables in Attachment 1 Part I the overall WHO Grade 3/4 Laboratory toxicities for pancreatic cancer patients and for patients with other tumor types is presented. Laboratory tests which are included for toxicity grading are: alkaline phosphatase, ALT, AST, bilirubin, BUN, creatinine, hemoglobin, WBC, segmented neutrophils, and platelets. The incidence of gr.3/4 toxicity by cycle is reported for (a) male pancreatic cancer patients \leq age 65, (b) male pancreatic patients >65 , (c) female pancreatic cancer patients \leq 65, or, (d) female pancreatic patients >65 . The number of patients at risk /cycle, median dose (mg/m^2)/cycle, the dose range /cycle (mg/m^2), number of patients with grade 3/4 toxicity/ cycle is reported using four dose ranges /cycle (< 800 mg, $800 - 3000$ mg, $3000 - 6001$ mg, and > 6001 mg). Laboratory toxicities for all other (non-pancreatic) cancer patients are presented. Tables which list the number of patients with grade 3/4 toxicity by age (≤ 65 or > 65 years) and gender by cycle are included. Each table contains the median dose in mg/m^2 , dose range (mg/m^2) per cycle, number of patients with gr. 3/4 toxicity in each of four dosing groups (< 800 mg, $800 - 3000$ mg, $3000 - 6001$ mg, and > 6001 mg).

The number of patients at risk in each of the four dose range groups are not presented. The number of patients and the percent gr. 3/4 toxicity are reported for each dose range. The percent is derived using the entire cohort (all patients at risk for that cycle) for the denominator rather than the number of patients in a specific dose range group. No population distribution is presented. As a result the incidence of serious toxicities in certain population groups is underestimated.

In evaluation of the incidence of grade 3/4 toxicity attention was focused on doses greater than $800 \text{ mg}/\text{m}^2$ since doses greater than $800 \text{ mg}/\text{m}^2$ will be used in practice and attention was focused on the first six to eight cycles since after this time the number of patients at risk becomes too small to draw any meaningful conclusions.

Review: Table 1 (pancreatic cancer patients) and Table 2 (other tumor type patients) provide information about the number of patients at risk and the median dose for each of the four groups as determined by age and gender.

Table 1: Number of Pancreatic Patients at Risk for Toxicity by Sex and Age with Median Dose / Cycle

Cycle	Males ≤ 65 yrs		Males > 65 yrs		Females ≤ 65 yrs		Females >65 yrs	
	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)
1	98	3000	45	4000	57	3250	44	4000
2	67	2750	29	3000	39	2509	26	2467
3	42	2663	21	2985	25	2500	19	2625
4	28	2750	15	2500	19	2379	13	2062
5	25	3000	9	3125	14	2625	9	2521
6	21	2985	7	3171	9	2500	6	2409
7	14	2894	6	3086	7	2000	2	2264
8	10	2500	3	2633	5	1500	2	2000

Table 2: Number of Non-Pancreatic Cancer Patients as Risk by Age and Sex with Median Dose per Cycle

Cycle	Male ≤ 65 yrs.		Male > 65 yrs.		Female ≤ 65 yrs.		Female > 65 yrs.	
	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)
1	305	2500	132	2500	220	2400	78	2400
2	261	3000	118	3000	183	2400	69	2572
3	185	3000	72	3000	118	2400	48	2500
4	138	3024	46	3000	96	2400	38	2450
5	90	3000	32	3475	62	2400	22	2467
6	58	3000	24	3525	39	3333	16	2749
7	31	3000	7	2033	13	2298	10	2250
8	25	3000	5	1208	11	2499	10	1735

In general after the first cycle the median dose in women of all ages is lower than in men. The percentage of patients who continue onto the next cycle of treatment is quite similar in all groups with both kinds of cancer. Men > age 65 have a greater degree of dose reduction / cycle after the first cycle as compared to men ≤ age 65. Women ≤ age 65 have a greater degree of dose reduction / cycle as compared to men ≤ age 65. Women > age 65 have the greatest degree of dose reduction of any group after the first cycle. Pharmacokinetic studies indicated reduced clearance in the elderly and in women with women > age 65 having about 50% less clearance than men ≤ age 65. The differences in the median dose in the various groups as well as the degree of dose reduction for patients in each of the four age / gender based groups support the

pharmacokinetic data. The information about the difference in median dose must be kept in mind when comparing the incidence of Grade 3/4 toxicities by age and sex in pancreatic cancer patients and patients with other tumor types.

No evidence of cumulative toxicity is seen with liver function studies (ALT, AST, alk. phosphatase, bilirubin) at any dose level in either sex at any age. No increase in gr. 3/4 alkaline phosphatase, bilirubin, or ALT is noted in any of the groups. Increased occurrence of gr. 3/4 AST elevation in men with pancreatic cancer > 65 as compared to men with pancreatic ≤ age 65. An increased occurrence of AST elevation in women with pancreatic cancer > age 65 is also noted. In patients with other tumor types women appear to have more early (cycle 1,2) gr. 3/4 toxicity than men. Renal function (BUN, creatinine) is not affected over time regardless of dose level. No difference in the incidence of toxicity is observed between any of the groups.

Gr. 3/4 hemoglobin toxicity is reported in all groups but no increase in toxicity is discernable in older patients or women as compared to men. Grade 3/4 leukopenia is reported for more cycles in a higher percentage of women as compared with men. The per cent incidence doubles over the first three cycles in women >65 with pancreatic cancer. An steady increase in grade 3/4 leukopenia is observed in women < age 65 with other tumor types. An increase in the incidence of grade 3/4 neutropenia is seen in women as compared to men despite the lower median dose. The figures suggest that gr. 3/4 neutropenia may be slightly more frequent in elderly women as compared to women ≤ age 65. Men >65 with pancreatic cancer have a lower incidence of grade 3/4 neutropenia as compared to their counterparts less than age 65. For other tumor types the incidence in men of all ages is the same and less than women in the same age group. With regard to grade 3/4 thrombocytopenia increased incidence is seen the both males and females > 65 years in cycle 1-3 as compared their counterparts less than age 65.

Attachment 1 Part 2:

This attachment deals with specific toxicities (WHO grade 3/4 diarrhea, hematuria, infection, nausea and vomiting, and proteinuria) for which causality was assigned (toxicity due to study drug) or causality was not assigned (toxicity possibly caused by study drug, but could be due to other factors). Table 3 and Table 4 contain information on the number of patients per cycle, the median dose (mg/m²) per cycle in each group: males ≤ 65, males > 65, females ≤ 65, and females > 65 years.

Review of Table 3 indicates that by treatment cycle the median dose in women is usually from 25-50% lower than their male counterpart. In Table 5 no difference in the median dose is observed in cycle one. After cycle one the median dose is frequently lower in women although not to the degree seen in the Causality Assigned group.

Table 3: Median Dose (mg/m²) and No. of Patients per Cycle with Grade 3/4 Clinical Toxicities, Causality Assigned

Cycle	Males ≤ 65 years		Males > 65 years		Females ≤ 65 years		Females > 65 years	
	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)
1	238	3000	71	3750	191	2400	65	2500
2	193	3000	56	3750	153	2400	45	2500
3	128	3000	44	3750	104	2400	39	2500
4	95	3360	27	3600	86	2400	30	2400
5	65	3000	19	3750	54	2450	17	3000
6	45	3000	15	3600	36	3000	13	3000
7	21	3000	3	3750	12	2149	6	1820
8	18	3000	1	4500	10	2250	6	1735

Table 4: Median Dose (mg/m²) and No. of Patients per Cycle with Grade 3/4 Clinical Toxicity, Causality Not Assigned

Cycle	Males ≤ 65 years		Males > 65 years		Females ≤ 65 years		Females > 65 years	
	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)
1	165	2404	106	2400	86	2400	57	2400
2	135	2969	91	2500	69	2400	50	2506
3	99	2880	49	2504	39	2504	28	3000
4	71	2892	34	2920	29	2379	21	2500
5	50	2998	22	2656	22	2187	14	2261
6	34	3087	16	2875	12	3346	9	2500
7	24	3315	10	2663	8	2854	6	2764
8	17	2404	7	3313	6	3455	6	2000

In reviewing toxicities the number of patient at risk per dose level range / cycle is not reported in any groups hence the relative number of serious toxicities can not be appreciated. No difference in the incidence of Grade 3/4 hematuria (three incidents), grade 3/4 proteinuria (six incidents), and grade 3/4 infections (fifteen incidents) is detected between groups. The incidence of nausea and vomiting is increased in all cycles in both causality assigned and causality nonassigned women ≤ age 65 despite lower median doses/cycle. Increased reporting by this population may be the reason or reduced drug clearance in women could be another reason. In women > 65 years the incidence of nausea and vomiting is similar to that of males > 65 and less than males ≤ 65. Surprisingly the incidence in elderly men and women is less than reported for males ≤ 65.

Possibly this reflects increased use of antiemetics in the > 65 age group. A slight increase in grade 3/4 diarrhea is seen in the males >65 and in women of all ages as compared to males ≤ age 65.

Attachment 1 Part 3:

In this section the Treatment Emergent Signs and Symptoms (TESS) are reported by age and sex for all patients in the ISS Database. In Table 5 the number of patient at risk per cycle by subgroup (males ≤ age 65, males > age 65, females ≤ age 65, and females > age 65) is reported.

Table 5: Median Dose (mg/m²) and Number of Patients at Risk by Age (≤ 65 , > 65 years) and Sex , TESS Data

Cycle	Males ≤ 65 years		Males > 65 years		Females ≤ 65 years		Females >65 years	
	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)	No. of Patients	Median Dose (mg/m ²)
1	430	2842	177	2941	277	2400	122	2402
2	329	3000	147	3000	222	2400	95	2500
3	226	3000	94	3000	143	2400	67	2500
4	167	3000	61	3000	115	2400	51	2400
5	115	3000	41	3171	76	2400	31	2521
6	79	3000	31	3450	48	3038	22	2500
7	45	3000	13	3000	20	2149	12	2250
8	35	3000	8	2473	16	2495	12	1735

The incidence of selected treatment emergent signs and symptoms [diarrhea, dyspnea, fever, flu syndrome, hematuria, infection, nausea, peripheral edema, rash, and vomiting] are reported for each of the above groups by dose ranges : < 800 mg/m², 800-3000 mg/m², 3001-6000 mg/m², and > 6001 mg/m². The incidence / cycle for the first six consecutive cycles is reported. After cycle six incidence may not be reported in some subgroups or incidence for a later cycle is reported. For each group (ie. male ≤ 65 years, male > 65.) for each cycle from 2- 32% of the TESS were reported without information about the dose of drug /cycle.

With regard to gastrointestinal -related signs and symptoms for the first six cycles, an increased incidence of nausea is observed over time in all four groups. A slightly higher incidence of nausea is noted in women especially women >65 years. The incidence of vomiting is less in men >65 years as compared to the other three groups. The incidence of vomiting is similar in men ≤ 65 years and women of all ages despite the 18-40% difference in median dose. With regard to diarrhea a definite increase in incidence is reported in those over sixty-five of both sexes as compared to those ≤ age 65. An increased incidence of diarrhea is seen in women as compared to men in cycles 1-3. The highest incidence is seen in women > 65 for cycles 1-3 and 6.

No difference in incidence of infection is noted when analyzed by sex and age. No difference is observed with regard to the incidence of "fever" or "flu syndrome". The incidence of dyspnea increases over the first six cycles in all groups. Dyspnea appears more often in the elderly in later cycles. Rash is most likely to occur in the first cycle of therapy (possibly explained by the use of premedication in subsequent cycles) and the incidence is similar in all groups. Peripheral edema occurs more frequently in the elderly and the incidence increases over successive cycles. No difference in incidence based on gender is noted. With regard to the incidence of hematuria no difference is detected between the four groups.

Attachment I Part 4:

The four section of this attachment presents data as to dose escalation, dose reduction, and dose omissions due by age for all cycles of therapy. In Table 6 the number (%) of patients ≤ 65 years or > 65 years who experience a change in dose is presented.

Table 6: Percentage of Injections/ Cycle in Patients \leq Age 65, $>$ Age 65 with Dose Escalations, Reductions, or Omissions

Cycle	Dose Escalation		Dose Reduction		Dose Omissions	
	Pts. ≤ 65 yrs.	Pts. > 65 yrs.	Pts. ≤ 65 yrs.	Pts. > 65 yrs.	Pts. ≤ 65 yrs.	Pts. > 65 yrs.
1	0.2	0.2	10.2	9.2	5.2	6.5
2	28.1	30.3	11.2	14.2	4.6	5.4
3	37.7	37.2	12.7	18.9	6.2	7.1
4	36.7	37.5	14.2	21.6	6.6	7.5
5	41.3	42.7	16.7	20.2	8.5	10.3
6	45.6	46.8	12.7	23.7	9.3	5.1
7	44.3	38.7	19.3	33.3	11.5	5.3
8	45.3	47.4	23.6	33.3	9.5	8.8

No difference in dose escalation is noted for those \leq age 65 and those over 65 years. Dose reductions occurred more often patients > 65 . The number of omitted doses is similar in both age group except for cycle 6.

Table 7 presents the three most common reasons for dose reduction for the first six cycles by age. No information about dose reduction by gender is provided. Table 8 present the major reasons for dose omission by age. Unfortunately the third most frequent reason given was "Comment" so that the actual reason for dose reduction is unknown.

Table 7: Three Most Common Reasons (%) for Dose Reductions by Age for Cycles 1-6

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65
Age												
REASON: Leukopenia	65.5	48.9	55.5	30.6	40.9	43.8	35.4	29.6	22.9	44.4	26.1	35.3
Thrombo- cytopenia	20.7	26.7	17.0	13.9	13.6	22.0	15.4	25.9	20.8	27.8	17.4	29.4
Comment	5.5	15.6	19.0	23.9	23.9	24.4	24.6	37.0	33.3	27.8	47.8	35.3

The most frequently given reason for dose reduction was leukopenia. In the ≤ 65 age group dose reduction for leukopenia is more common than in the > 65 age group. The number of omitted doses due to leukopenia is similar in both groups. In the elderly dose reduction for thrombocytopenia occurred more often. Thrombocytopenia was also a more frequent cause of dose omission in the elderly. No information was provided for age and gender.

Table 8: Four Most Common Reasons for Dose Omission by Age for Cycle 1-6

	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65	≤ 65	> 65
Age												
REASON: Leukopenia	29.2	28.8	15.8	17.9	18.6	9.1	7.3	—	10.2	33.3	11.4	25.4
Thrombo- cytopenia	4.2	10.2	2.6	20.5	1.4	12.1	7.3	3.8	8.2	4.5	14.3	—
Comment	25.8	25.4	40.8	25.6	55.7	33.3	40.0	46.2	40.8	40.9	42.9	55.9

Attachment 2:

In this section the data tables to support the Adverse Reactions section of the label were presented. These data were reviewed and provide correct information about the incidence of adverse reactions.

Attachment 3:

This attachment contains copies of the references cited in the label.

Summary of Safety Information:

From the information contained in the Safety Review Amendment gemcitabine is **not as well tolerated in the elderly and women as compared to males ≤ age 65**. Information on differences in median dose, increased dose reduction in persons > age 65, an increase in certain toxicities despite a reduction in median dose for a particular group support a difference in tolerability based on gender and age. Since the number of patients in each dose range group for

each cycle is not presented the extent to which certain toxicities are increased in each subgroup (male \leq age 65, male $>$ 65, females \leq age 65, and females $>$ 65 can not be accurately estimated..

Action:

Eli Lilly will be requested to provide the number of persons at risk in each subgroup/cycle so that a better appreciation of the degree of toxicity in certain population groups (women \leq and $>$ age 65 and men $>$ 65). The applicant will also be requested to provide information about the dose reduction by gender in patients \leq and $>$ age 65.

Comment #2: LABELLING COMMENTS

Comment 2a.: In the Clinical Studies Section Sentence three, paragraph one should be changed from _____ to "**A second trial studied the use of Gemzar® in pancreatic cancer patients refractory to _____**" In the protocol for JHAY no "allowed" FU regimens were specified.

Applicant's Response: The applicant accepts the revision as proposed by the agency.

Agency Comment: Delete _____ and substitute "**previously treated**". In a fax dated 4/15/96 Eli Lilly agrees to delete _____ and substitute "**previously treated**".

Comment 2b.: Sentence one, paragraph two which reads _____

"**The primary efficacy parameter in these studies was clinical benefit response which _____ based on analgesia consumption, pain intensity, performance status and weight change. Definitions for improvement in these variables _____**"

Applicant Response: The applicant accepts the revision with the following addition:

"Definitions for improvement in these variables were formulated **prospectively during** _____

FDA Response: FDA agrees with the inclusion of this phrase in the Clinical Studies section. In addition the underlined phrases need to be added whenever Clinical Benefit Response is defined since the definition for Clinical Benefit Response changed after week 12 on study.

"The primary efficacy parameter in these studies was clinical benefit response which is a

The applicant may desire to reword this paragraph with the understanding that Clinical Benefit Response as defined in the protocol must be included in the label.

Comment 2c.: The sentence in section ii) which reads _____

_____ **"the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain _____ not due to fluid accumulation."** The sponsor has not provided

Applicant's Response: The applicant accepts this revision with the addition of the following phrase (indicated by bolded italicized letters):

"the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain _____ not due to fluid accumulation."

FDA Response: FDA agrees with inclusion of the additional phrase.

Comment 2d.: In the third paragraph of the Clinical Studies section the following sentences should be changed from _____

Applicant's Response: The applicant accepts the change proposed by the agency with the addition of the following phrase:

FDA Response: FDA agrees with the proposed change in wording.

Comment 2e.: In Table 3 on page 6, the following changes should be made:

- i. _____

- ii. _____

- iii. _____
- iv. _____

- v. _____

- vi. _____

Applicant's Response: Lilly sent a revised data table using different point estimates and ranges. Lilly requested that the survival probabilities continue to be included in this table. Lilly requests that the range for the various point estimates be omitted. The applicant did omit the response rate information.

FDA Response: The agency has requested a printed copy of the applicant's data sets for JHAY and JHAZ. All dates will be checked against the Agency's data set and any discrepancies checked against the case report forms. A copy of the corrected data set will be provided to the applicant. The point estimates, ranges, confidence intervals, and Kaplan Meyer curves will be recalculated using this data set. A copy of the agency's final data set will be provided to the applicant and as an amendment to the medical officer's NDA review. The statistics from this review will be used in the label.

With regard to inclusion of the survival probabilities and ranges in the label the agency requests that the Kaplan-Meyer survival curve be used in place of survival probabilities for any particular time point for both studies (JHAY and JHAZ) since this is the most accurate presentation to the data. Likewise the most accurate presentation of the course of Time to Progression and the Time to Treatment Failure would be a Kaplan-Meyer plot. The applicant notes that survival

probabilities were used in the Intron A labeling. These probabilities were based on cohort of 278 patients followed for > 8 years. In the Nalvelbine label the statistics were based on a study population greater than 600 patients. Survival probabilities for Gemzar at one year reflect information on five patients who had difference stages of disease at study entry.

Comment 2f.: In the next paragraph the following sentence: _____

The sentence might be better worded as follows:

Applicant's Response: Lilly agrees to accept the proposed wording.

Agency Comment: Several times in the Clinical Studies section (paragraph 1, sentence 2; paragraph 5) _____ is used. The data in the CRFs did not document _____

_____ **must be**
deleted unless the applicant can provide documentation of: _____ state for all patients enrolled on JHAZ: _____

Comment 2g.: In Table 4, the following changes should be made based on the statistics done by the agency:

- i. Delete the: _____
- ii. _____
- iii. _____
- iv. _____

- v. _____

vi. _____

vii. _____

Applicant's Response: The applicant agrees to remove the tumor response data. The applicant requests a copy of the time to event data (SAS data set). The applicant requests that the time to event data be measured in months rather than days.

FDA Comment: Please see the comments in section 2e. regarding the statistics..

Comment 2h.: The following sentences should be revised:

Applicant's Response: The applicant had decided to delete this paragraph from the label.

Comment #3: In the Indications and Usage Section:

Applicant's Response: The applicant agrees to delete the comment.

Comment #4: In the Warnings Section, a statement should be added about the possibility of

Hemolytic-Uremic Syndrome particularly in patients with preexisting renal impairment.

Applicant's Response: The applicant declines to include a statement in the Warning Section about the possibility of HUS (Hemolytic-Uremic Syndrome) since the reported incidence is only 0.25% and only two patient required dialysis.

Agency Response: Since the actual incidence is likely to be under reported and some patients may not have full blown HUS, a sentence **MUST** be placed in the Warning sections.

Comment #5: In the Laboratory Tests Subsection, a phrase indicating that renal and hepatic function should be evaluated prior to initiation to therapy with Gemcitabine should be included.

Applicant's Response: The applicant agrees to revise this sentence as follows:

"Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter."

Comment #6: In the Precautions Section, the following changes are necessary:

- a. The pregnancy category is incorrect. See pharmacology review.
- b. A section entitled Drug Interactions needs to be included with information provided about recognized drug interactions, if known. (See Biopharm comments.)

Applicant's Response: The applicant agrees to "**Pregnancy Category D**" classification as required by the Agency for chemotherapeutic agents. The applicant agrees to add a section for drug interaction which reads as follows:

FDA Response: The agency agrees with the applicant's addition to the label.

Comment #7: The Adverse Reactions Subsection, as written, does not accurately describe the toxicities of Gemcitabine. The information contained in this section can not be verified from the NDA. The following information should be included in this section in tabular form:

- a. A table must be included which lists all the common toxicities which were graded using the WHO Common toxicity criteria and reported for Gemcitabine, the number of and % incidence of each of these toxicities in the 979 patients treated on the weekly schedule, the number of and % incidence of the same toxicities in the

244 pancreatic cancer patient data base along with the number and % incidence of Grade III/IV toxicity in this population. If the sponsor wishes to include the information on the group of 565 patients who had only drug related toxicities graded, another column containing the results from this group can be added to the table.

- b. A brief narrative about specific toxicities must include information about how the overall incidence of each toxicity (number / number at risk, %) and the % with each grade of toxicity were determined. Continue to include in the narrative a description of study discontinuations and life threatening adverse reactions.

Applicant's Response: The applicant has included *Table 5: Selected WHO-Graded Adverse Events in Patients Receiving Gemzar*" which includes listings for all toxicities with a greater than 10% incidence in all patients and a separate listing for pancreatic cancer patients. Information about the number of patients discontinued due to AEs is included in the table. The data in this table is accurate and acceptable to the agency.

In the narrative portion of the Adverse Reaction section the following sentences **MUST** be revised:

1.) In the *Hematologic* section delete the sentence : _____
_____. The sponsor may wish to replace this with a phrase such as: _____

2.) In the *Gastrointestinal* subsection **delete** the following sentences: _____

3.) In the *Pulmonary* section **delete** the following sentences: _____

_____ to read: "**Rarely pulmonary**" _____

4.) In the "*Flu-like Symptoms*" subsection delete the following sentence: _____

5.) In the *Neurotoxicity* section **amend** the following sentence _____
_____ to read _____

Comment #8: In the Adults Subsection, delete paragraph 4 which reads _____

Applicant's Response: The applicant agrees to delete this sentence.

Comment #9: In the Elderly Patients Subsection, provide evidence to prove that Gemzar® is well tolerated in the elderly by relating total dose mg/m² with the occurrence of toxicity. The data provided in the NDA is not adequate to determine if Gemcitabine, at the dose recommended in the label, is safe in the elderly. Information must be provided about the total dose per cycle, number of dose reductions or missed doses per cycle, and total dose of drug in mg/m² administered in patients >65 as compared to patients age 65 or less. Analyses which relate total dose, doses per cycles, and degree of toxicity should be provided by sex and age (males ≤65, males >65, females ≤65, females >65) since clearance is markedly reduced in females and patients greater than age 65.

See **Comment # 1** for evaluation of safety in the elderly. The applicant proposes that the following paragraph be added to the Precautions section :

and the applicant proposes to remove any comment about the reduced clearance the women and the elderly from the Dosage and Administration section. The applicant proposed removal the caution about Gemzar^R patients with hepatic and renal failure from the Dosage and Administration section.

Agency Comment: DELETE the first sentence :

Include information in this section about the increased frequency of thrombocytopenia in the elderly as compared to patients under sixty-five. The agency notes on review of the safety data that the median dose per cycle was decreased by 18 - 40% in women of all ages as compared to men, but the incidence (%) toxicity per cycle was similar or increased in women as compared to men. The incidence of dose reductions for all cycles after cycle 1 was greater in the elderly than in those less than age 65. No information about dose reduction by gender was provided in the safety amendment. The agency requests information about the incidence of dose reduction / omission per cycle for the following groups: men ≤ age 65, men > age 65, women ≤ age 65, and women > age 65.

Comment # 10: The Subsection title Children should be retitled Pediatric Patients in keeping with the regulations.

Applicant's Response: The applicant has decided to omit the subsection labelled _____ from the **Dosage and Administration Section** since Gemzar has not been approved for use in the _____. In the **Precautions** section of the label the sponsor proposes the following subsection:

"Pediatric Patients: Gemzar has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established."

Applicant's Response: The labeling change is acceptable to the Agency.

Comment # 11: In the **References** Section, references no. _____ should be deleted.

Applicant's Response: The applicant has deleted the original _____, and has added eight new references. The applicant is advised to **delete** _____ and to have the citations noted in the label available on request.

Comment # 12: The applicant has deleted _____ from the **Overdosage** section and has substituted human data.

Agency Response: The substitution of data about human doses of 5700 mg/m² is acceptable.

II. REVIEW: APPLICANT'S RESPONSE to CLINICAL COMMENT from FOUR MONTH SAFETY UPDATE REVIEW

Comments Transmitted to Applicant:

1. In order to determine if an increase in adverse events has occurred over this reporting period, information should be provided on the total number of patients at risk (under treatment) for each of the adverse events reported during this one hundred twenty day period.
2. Please provide additional information about all patients who have received Gemcitabine with concurrent radiation therapy. How many patients have been treated with radiation while on Gemcitabine? Information about the type and stage of malignancy, the amount of Gemcitabine exposure in mg/m², the type and dose of radiation therapy which was given in combination with Gemcitabine therapy, and the type, nature, and duration of the toxicity(s) observed is requested. If significant potentiation of toxicity is found when full dose Gemcitabine is used in combination with certain types of radiation therapy this information must be included in the label.

Review of Applicant's Response:

Comment #1: Eli Lilly has submitted a listing in tabular form which shows no increase in the incidence of adverse reactions in the 733 patients treated from 1/01/95-5/0195 as compared to the 2884 patients treated form 3/01/83-5/01/95. The applicant concludes that no new information has appeared which would require revision of the labeling.

FDA Response: The agency agrees that no new adverse reactions and no increase in adverse reactions were reported during the first Safety Update.

Comment #2: The applicant reviewed the electronic data base which includes 1126 patients. No information on radiotherapy was available on 544 patients. Of the remaining 582 patients, thirty-one received radiotherapy either during or on completion of therapy with gemcitabine. The 39 therapies were palliative in nature. Serious adverse events were reported in twenty-six of the thirty-one patients. Twenty-one of these twenty-six SAEs were deaths due to tumor progression. Four of the five remaining SAEs were not related to the use of gemcitabine and RT. In one case the concomitant use of gemcitabine with thoracic radiation may have been responsible for the increased severity of esophagitis. On four occasions one dose of gemcitabine was omitted during RT.

The applicant acknowledges that the concomitant use of "radical" radiotherapy (60 Gy over 6 weeks) and gemcitabine 1000 mg/m² weekly has been associated with severe toxicity. Concurrent gemcitabine 300 mg/m² weekly was used with 2.0 Gy/day, five times per week for seven weeks in patients receiving extracranial irradiation for head and neck cancers. In the first five patients acute toxicities (RTOG Toxicity Grading) include grade 3 skin toxicity (4/5), grade 2 mucositis (4/5), and grade 2 pharyngeal toxicity (4/5). Lilly proposes to include the following statement in the labeling in the **Clinical Studies** section:

and the following subsection will be added to the end of the **Precautions** section:

"The _____ regimen for safe administration of Gemzar with therapeutic doses of radiation has not yet been determined _____"

FDA Response: The agency concurs with the applicant's proposals for inclusions in the labeling about possible potentiation of toxicity with concurrent full dose RT and gemcitabine.

ACTION(S):

1. The additional information in the gemcitabine safety review indicates that the gemcitabine is less well tolerated in patients >65 and in women as compared to men. No change in the recommended dosage is indicated but the **Dosage and Administration** section of the label will contain information to indicate the possibility of increased toxicity at the recommended doses.
2. The labelling revisions/changes were reviewed. See the Problem List for those areas (*Comment # 2a, 2c, 2e, 2g, 4,7, and 11*) of the label which will need further revision.
3. The additional information with regard to the four month safety update is adequate. No new adverse reactions were reported. No increased incidence of adverse events were noted during this reporting period in comparison to previous reporting periods.

COMMENTS TO BE TRANSMITTED TO APPLICANT:

A. With regard to the Safety Review Eli Lilly is requested to provide the number of persons at risk in **each dose range group** in **each subgroup** / cycle for the following Tables:

AST	Tables 1.2. 3	a,b,c,d-Cycles 1-4
	Tables 1.3. 3	a,b,c,d- " "
Leukocytes	Tables 1.2. 8	a,b,c,d-Cycles 1-8
	Tables 1.3. 8	a,b,c,d- " "
Neutrophils	Tables 1.2. 9	a,b,c,d-Cycles 1-8
	Tables 1.3. 9	a,b,c,d- " "
Platelets	Tables 1.2.10	a,b,c,d,-Cycles 1-8
	Tables 1.3.10	a,b,c,d- " "
Hemoglobin	Tables 1.2. 7	a,b,c,d- Cycles 1-6
	Tables 1.3. 7	a,b,c,d- " "
Nausea & Vomiting	Tables 2.2.4.	a,b,c,d-Cycle 1-8
	Tables 3.7.	a,b,c,d-Cycle 1-8
	Tables 3.10	a,b,c,d-Cycle 1-8
Diarrhea	Tables 3.1	a,b,c,d -Cycles 1-6
Rash	Tables 3.9	a,b,c,d-Cycles 1-6
Peripheral Edema	Tables 3.8	a,b,c,d-Cycles 1-6
Dyspnea	Table 3.2	a,b,c,d-Cycle 1-8

in order to provide a better understanding of the degree of toxicity in certain population groups (women \leq and $>$ age 65 and men $>$ 65).

The applicant is requested to provide information about the dose reduction by gender in patients \leq and $>$ age 65. (Tables 4.2 and 4.3)

B. Labeling Comments:

The following areas of the label need further revision. (The original comment, the applicant's response, and the agency's answer to the applicant's response are included for clarity.)

1) *Comment #2a:* In the Clinical Studies Section Sentence three, paragraph one should be changed from _____ to "**A second trial studied the use of Gemzar® in pancreatic cancer patients refractory to _____**". In the protocol for JHAY no "allowed" FU regimens were specified.

Applicant's Response: The applicant accepts the revision as proposed by the agency.

FDA RESPONSE: Delete _____ and substitute "**previously treated with FU**". In the Clinical Studies section (paragraph 1, sentence 2; paragraph 5; title to Table 4) the phrase _____ is used. Since the data in the CRFs did not document FU refractoriness for the patients, _____

_____ : **must be deleted** _____

_____ Since all patients had been treated with FU or FU combinations, use of a phrase "*Gemzar in Patients Previously Treated* _____" the correct way to describe the JHAZ enrollees..

2) *Comment 2c.:* The sentence in section ii) which reads _____

_____ must be changed to: "**the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (_____ not due to fluid accumulation.**" The sponsor has not provided data to prove that caloric intake _____

The applicant accepts this revision with the addition of the following phrase (indicated by bolded italicized letters):

"the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain _____ not due to fluid accumulation."

FDA RESPONSE: FDA agrees with the inclusion of this phrase in the Clinical Studies section.

In addition the underlined phrases need to be added whenever Clinical Benefit Response is defined since the definition for Clinical Benefit Response changed after week 12 on study. *"The primary efficacy parameter in these studies was clinical benefit response which is a composite measure of*

— The applicant may desire to reword this paragraph with the understanding that Clinical Benefit Response as defined in the protocol must be included in the label.

3) *Comment 2e.*: In Table 3 on page 6, the following changes should be made:

- i. _____

- ii. _____

- iii. _____
- iv. _____

- v. _____

- vi. _____

FDA RESPONSE The agency requested [in a Telecon held on March 27, 1996] a printed copy of the applicant's data sets for JHAY and JHAZ. All dates will be checked against the Agency's data set and any discrepancies checked against the case report forms. A copy of the corrected data set will be provided to the applicant. The point estimates, ranges, confidence intervals, and Kaplan-Meier curves will be recalculated using this data set. A copy of the agency's final data set will be provided to the applicant and as an amendment to the medical officer's NDA review.

With regard to inclusion of the survival probabilities and ranges in the label the agency requests that a Kaplan-Meier survival curve be used in place of survival probabilities for both JHAY and JHAZ since this is the most accurate presentation to the data. Likewise the most accurate presentation of the course of Time to Progression and the Time to Treatment Failure would be a Kaplan-Meier plot. Once the accuracy of the data set is confirmed, plots generated by both the applicant and the agencies should be the same. No response rates will be included in the table.

- 4) *Comment #2g:* _____

- i. _____
- ii. _____
- iii. _____
- iv. _____

- v. _____

- vi. _____

- vii. _____

FDA RESPONSE: Please see the comments in section 2e. regarding the statistics.

- 5) *Comment #4:* In the Warnings Section, a statement should be added about the possibility of Hemolytic-Uremic Syndrome particularly in patients with preexisting renal impairment.

FDA RESPONSE: The applicant has declined to include a statement in the Warning Section about the possibility of HUS (Hemolytic-Uremic Syndrome) since the reported incidence is only 0.25% and only two patient required dialysis. **A sentence must be placed in the Warnings section.**

6) *Comment #7:* The Adverse Reactions Subsection, as written, does not accurately describe the toxicities of Gemcitabine. The information contained in this section can not be verified from the NDA. The following information should be included in this section in tabular form:

- a. A table must be included which lists all the common toxicities which were graded using the WHO Common toxicity criteria and reported for Gemcitabine, the number of and % incidence of each of these toxicities in the 979 patients treated on the weekly schedule, the number of and % incidence of the same toxicities in the 244 pancreatic cancer patient data base along with the number and % incidence of Grade III/IV toxicity in this population. If the sponsor wishes to include the information on the group of 565 patients who had only drug related toxicities graded, another column containing the results from this group can be added to the table.
- b. A brief narrative about specific toxicities must include information about how the overall incidence of each toxicity (number / number at risk, %) and the % with each grade of toxicity were determined. Continue to include in the narrative a description of study discontinuations and life threatening adverse reactions.

FDA RESPONSE: The applicant has included *Table 5: Selected WHO-Graded Adverse Events in Patients Receiving Gemzar*" which includes listings for all toxicities with a greater than 10% incidence for all patients and for pancreatic cancer patients as well as the number who discontinued therapy due to the side effects. The data in this table is accurate and acceptable to the agency.

In the narrative portion of the Adverse Reaction Section the following sentences must be revised:

1.) In the *Hematologic* section delete the sentence : _____
_____. The sponsor may wish to replace this with a phrase such as: _____
_____.

2.) In the *Gastrointestinal* subsection delete the following sentence: _____
_____.

3.) In the *Pulmonary* section delete the following sentences: _____
_____. Amend the following sentence: _____ read:

_____.

4.) In the *"Flu-like Symptoms"* subsection delete the following sentence: _____
_____.

5.) In the *Neurotoxicity* section **amend** the following sentence _____
_____ to read _____

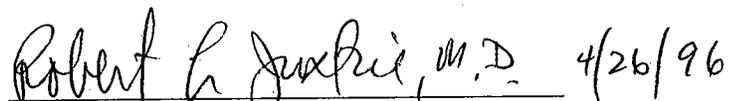
6) **Comment # 12:** The applicant has deleted _____ and has substituted human data.

Agency Response: The substitution of data about human doses of 5700 mg/m² is acceptable.

7) **Comment # 11:** In the References Section, _____ should be deleted.

FDA RESPONSE: The applicant has deleted the original 38 references and has added eight new references. The applicant is advised to **delete** _____ and to have all citations available on request.


Genevieve A. Schechter, M.D.
Medical Reviewer-DODP


Robert L. Justice, M.D.
Group Leader-DODP

Orig.: NDA20509
cc: HFD-150/Div.File
HFD-150/G.Schechter
HFD-150/L.McCollum

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

ENVIRONMENTAL ASSESSMENT/FONSI

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-509

Gemzar (gemcitabine hydrochloride)

**DIVISION OF ONCOLOGY DRUG PRODUCTS
(HFD-150)**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-509

Gemzar (gemcitabine hydrochloride)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food And Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The FDA, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Gemzar (gemcitabine hydrochloride), Eli Lilly and Company, has prepared an abbreviated environmental assessment (EA) for a drug in the prevention, treatment, or diagnosis of a rare disease or similarly infrequent use (21 CFR 25.31a(b)(3) (attached)). An abbreviated EA is appropriate given that _____

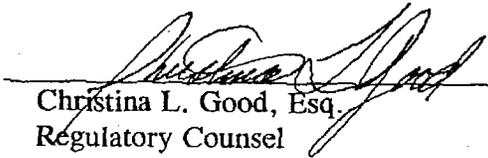
_____ The EA evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Gemzar is a drug for the treatment of adenocarcinoma of the pancreas. The finished drug product will be primarily used by physicians at hospitals and on an outpatient basis. Because of the total annual use in the United States will be less than _____

_____ Precautions at the manufacturing facilities also are expected to minimize occupational exposures and environmental release. Accidental spill control procedures are available. Disposal will be in accordance with appropriate waste procedures. Adverse effects are not anticipated upon endangered species or historic sites listed in or eligible for listing in the National Register of Historic Places.

CDER has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects.

2/23/96
DATE


Christina L. Good, Esq.
Regulatory Counsel
Environmental Assessment Team
Center for Drug Evaluation and Research

3/4/96
DATE


Concured
Nancy Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachment:

FOI Copy of Environmental Assessment for Gemzar (gemcitabine hydrochloride)

**ENVIRONMENTAL ASSESSMENT
FOR THE USE OF GEMZAR®
IN THE TREATMENT OF PANCREATIC
CANCER**

**Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285**

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**ENVIRONMENTAL ASSESSMENT
FOR THE USE OF GEMZAR®
IN THE TREATMENT OF PANCREATIC CANCER**

- | | |
|---------------------|---|
| 1. DATE | October 1995 |
| 2. APPLICANT | Eli Lilly and Company |
| 3. ADDRESS | Lilly Corporate Center
Indianapolis, Indiana 46285 |

4. DESCRIPTION OF THE PROPOSED ACTION

Eli Lilly and Company is seeking approval for the use of Gemzar® in the treatment of adenocarcinoma of the pancreas. The active ingredient in Gemzar is gemcitabine hydrochloride. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis. Gemzar will be available in vials containing 200 mg or 1 g of gemcitabine (expressed as free base) in the form of a _____ Gemzar may be administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks. This would be followed by a week without treatment. Additional treatment cycles of once per week for three weeks at the same dose, with a week off of treatment, could then be provided. Dosage reduction is applied based on the amount of any toxicity experienced by the patient.

This environmental assessment was developed to address the potential environmental issues associated with the use of this pharmaceutical in the treatment of pancreatic cancers. Approval of this new drug would authorize the production of gemcitabine hydrochloride at Tippecanoe Laboratories of Eli Lilly and Company (Lilly Road, Shadeland, IN 47905). Gemzar will be formulated and packaged at facilities of Eli Lilly and Company in Indiana (1555 Kentucky Ave., Indianapolis, IN 46221) and at Lilly France, S.A. (Rue du Colonel

Lilly, 67640 Fegersheim, France). Gemzar will be administered in hospitals and on an outpatient basis throughout the United States and could potentially be introduced into the following environments:

- a. The environments adjacent to the manufacturing, formulation, and packaging plants. The manufacturing plant in Indiana is located in a temperate climate and in a rural setting. The formulation and packaging plant facilities in Indianapolis are in an urban setting. These facilities in France are in a temperate climate and a rural setting.
- b. Sewage treatment facilities throughout the United States receiving wastes from hospitals and clinics where Gemzar is used.
- c. Septic tanks receiving wastes from patients at their homes after outpatient treatment.

Drug substance and product that are off-specification, returned, expired, or otherwise unused will be disposed of at licensed incineration facilities. In the United States, this material will be incinerated at the following facility according to a Resource Conservation and Recovery Act permit issued by the U.S. EPA under facility identification number IND072040348:

Eli Lilly and Company
State Road 63
Clinton, IN 47842

In Europe, material that is returned to the Fegersheim facility or generated by that facility will be disposed of at the following industrial incinerator facility, which has two Prefectoral permits (approved May 14, 1985 and December 9, 1987) for industrial and chemical wastes:

5. IDENTIFICATION OF THE CHEMICAL SUBSTANCE

A. FORMULATION

Gemzar will be available in vials containing 200 mg or 1 g of gemcitabine hydrochloride (expressed as gemcitabine free base). Gemzar will be in the form of a sterile lyophilized material. To reconstitute, at least 5 ml of 0.9% Sodium Chloride Injection is added to the 200-mg vial or at least 25 ml of 0.9% Sodium Chloride Injection is added to the 1-g vial. Chemicals used to manufacture the drug substance are listed in a confidential attachment (Attachment I).

B. GEMCITABINE HCl

Gemcitabine HCl is a white to off-white solid. _____ chemical process is required to produce this drug substance. Specifications indicate that the bulk drug substance is not less than _____ gemcitabine hydrochloride with not more than _____ of any one related substance, or not more than _____ of total related substances.

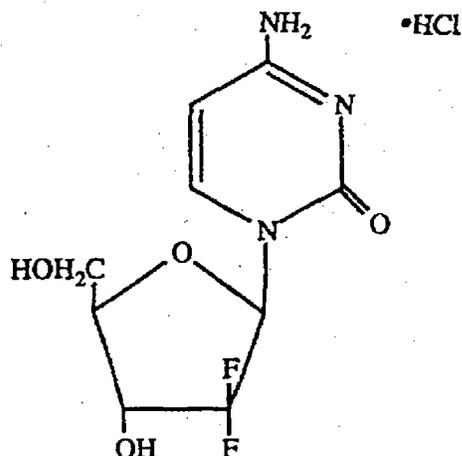
Chemical Name: 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer)

Molecular Formula: $C_9H_{11}F_2N_3O_4 \cdot HCl$

CAS Registry Number: 122111-03-9

Molecular Weight: 299.66

Structural Formula:



Vapor Pressure: Gemcitabine HCl is a nonvolatile solid. Thermogravimetric analysis showed no weight loss until about 208°C.

Melting Temperature: Gemcitabine HCl did not melt, but decomposed at 230.4 ± 0.4°C.

Dissociation Constant: pKa = 3.58

Ultraviolet-Visible Absorption Spectrum: One peak maximum was observed at 268-269 nm for 6.7 x 10⁻⁵ M solutions of gemcitabine HCl. Mean absorbances at pH 5, 7, and 9 were 0.616, 0.606, and 0.576, respectively. Mean molar extinction coefficients at pH 5, 7, and 9 were 9200, 9023, and 8520 L/mole-cm, respectively.

Solubility in Water at 25 °C:

Average pH	Equilibrium Solubility (mg/ml)
5	16.0 ± 0.3
7	15.3 ± 0.4
9	15.8 ± 0.4

Octanol/Water Partition Coefficient:

Solution pH	Octanol/Water Partition Coefficient
5	0.053 ± 0.001
7	0.053 ± 0.001
9	0.052 ± 0.001

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. INTRODUCTION OF SUBSTANCES FROM THE MANUFACTURING SITES

1. Facilities Used for Manufacturing, Formulating, and Packaging

The processes for manufacturing gemcitabine hydrochloride, the operations for formulating and packaging Gemzar, and the pollution control practices at the corresponding plant sites are designed to result in minimal environmental impact. The production of gemcitabine hydrochloride will occur at the Tippecanoe production facilities of Eli Lilly and Company near Lafayette, Indiana (Lilly Road, Shadeland, IN 47905). Gemzar will be formulated and packaged at the facilities of Eli Lilly and Company in Indiana (1555 Kentucky Ave., Indianapolis, IN 46221) and at Lilly France, S.A. (Rue du Colonel Lilly, 67640 Fegersheim, France). Production of gemcitabine hydrochloride will be done under Good Manufacturing Practices. Eli Lilly and Company will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at all production, formulation, and packaging facilities. Eli Lilly and Company will also comply with applicable occupational requirements (ie. OSHA) at the Federal, State, and local levels.

2. Environmental Regulatory Requirements

Treatment, storage, and disposal practices for solid, liquid, and gaseous wastes from the Indiana plant site are defined by the regulations administered, in certain instances, by the U.S. Environmental Protection Agency (EPA) and in other instances, by the Indiana Department of Environmental Management (IDEM). Permits related to the manufacturing, formulating, and packaging of gemcitabine are issued by these regulatory agencies for the discharge of wastewater (NPDES), the treatment, storage, and disposal of materials (RCRA), and air emissions (AIR). In addition to the federal and state regulatory agencies, the Indianapolis Department of Public Works (DPW) issues permits related to the discharge

of wastewater to the municipal wastewater treatment facilities. Eli Lilly and Company has made application or will make application for all necessary environmental permits to manufacture gemcitabine. The environmental permits associated with gemcitabine hydrochloride are listed below.

Location	Permit Number	Expiration
Tippecanoe	NPDES IN0002861	9/30/92*
	RCRA IND006050967	4/30/93*
	AIR 79-04-90-0382	4/01/90*
	AIR CP 157-1891	8/16/98
	AIR CP 157-2682	N/A**
	AIR CP 157-2593	N/A***
	AIR CP157-1980	7/13/97
Indianapolis	DPW 283001	12/31/95
	DPW 283004	12/31/95

* A condition of the permit stipulates that the permit remains in force until the regulatory agency issues a new one, as long as timely application (90 days prior to expiration for air permits and 180 days prior to expiration for water and RCRA permits) for a new permit is made before the expiration date.

** This is a permit which has no expiration date.

*** This is a construction permit which has no expiration date. Upon completion of construction, the operating permit will be validated and an expiration date will be issued.

NOTE: In addition, the Tippecanoe facility also has a facility air identification number OP157-00006 with the Indiana Department of Environmental Management.

Formulation of Gemzar in Fegersheim, France will be performed in accordance with the pertaining environmental control laws of France, especially Nr. 76-663 published on July 19, 1976, as implemented by national and local authorities. A certification of Good Pharmaceutical Manufacturing Practices at this facility provided by the Social Affairs and Employment Ministry is in a confidential attachment (attachment 1). A confirmation of

the resulting gases will be _____ The remaining scrubber solution will be sent through biological treatment. Trace amounts of solvent may appear in the stream sent to biological treatment.

The chemical wastewater treatment facility is primarily composed of two air activated sludge tanks having a combined aeration volume of 15.9 million gallons (a 7.8 million gallon aeration tank and a 8.1 million gallon aeration tank). The 7.8 million gallon tank is the first in the series, is operated to have a hydraulic retention time of _____ hours, and is aerated with 224 aerators with a submerged air flow of 3,000 SCFM. The 8.1 million gallon tank is operated to have a hydraulic retention time of _____ hours and is aerated with 364 aerators with a submerged air flow of 4,500 SCFM. These systems are designed such that the actual retention time and air flow of these units can be adjusted to compensate for changes in flow and waste strength. Trace organics that enter this system are oxidized and come into contact with the microorganisms that can metabolize the compounds or use them as an energy source.

Effluent from these units are processed in clarification systems. The three clarification units that support the air activated sludge tanks have been designed with an overflow rate of 242 gal/day/ft² at a flow rate of 6,785,760 gal/day. Sludges from these units are thickened, dewatered, and digested before proper disposal.

The Tippecanoe wastewater facility treats materials to achieve BOD and COD levels well below NPDES permit limits. The average daily COD and BOD effluent limits for the entire facility are 38,962 pounds and 7,730 pounds, respectively. The entire facility discharges 10.5 million gallons of wastewater each day. Effluent pH is consistently maintained within the permit limits for pH of the discharge (between 6.0 and 9.0). In general, less than one percent of the daily discharge of wastewater from this facility will be attributed directly to gemcitabine hydrochloride manufacturing. The Tippecanoe facility effluent is discharged into the Wabash River.

intent to comply with environmental regulations governing the manufacture of Gemzar from this facility is included in another confidential attachment (attachment 2).

Gemcitabine hydrochloride is produced in a multi-step chemical process. A list of materials used in the processes is in a confidential attachment (Attachment 3). The disposition of materials used, consumed, and produced in the process steps to manufacture gemcitabine hydrochloride is described in another confidential attachment (Attachment 4). In the fifth year of production, it is anticipated that fewer than— batches of gemcitabine will be needed for world-wide use. Emissions from production and formulation of gemcitabine will be less than 1 percent of the entire emissions already permitted for each of the facilities where this material will be produced.

3. Wastestream Treatment, Control, and Handling

a. Wastes from Manufacturing

Releases into the environment of wastewater pollutants and liquid and solid wastes resulting from the production of gemcitabine hydrochloride will be controlled. Liquid process waste streams directly from the chemical synthesis of gemcitabine will either be recovered for reuse, treated by thermal oxidation, or treated by biological wastewater treatment. Solids and particulate filters will also be collected for incineration. Certain solids may also be recycled or disposed of at approved solids disposal facilities. Dilute wash waters from production processes will be thermally oxidized or treated in biological wastewater treatment facilities. Gemcitabine hydrochloride will be produced in facilities already designed and being operated for the production of human drugs. Emission control equipment and treatment systems are or will be in place for these manufacturing operations.

At the Tippecanoe facility, waste gases from the process will be captured by liquid scrubbers, vented to a carbon absorber, vented to a condensor, or vented to a regenerative thermal oxidizer. This point source control equipment achieves the permitted 90 to 95% control required for volatile compounds. Spent scrubber solution can be air stripped, and

Two separate liquid thermal oxidizers at the Tippecanoe facility are designed to oxidize two types of liquid wastes: primary waste and secondary waste. Primary wastes are mainly spent solvents and are capable of supporting autonomous combustion in the primary combustion chamber. Secondary wastes are mainly water and are injected into the main oxidation chamber for thermal destruction downstream from the primary waste, at a distance sufficiently far so as to not affect the primary burner flame. These thermal oxidizers are designed to achieve 99.99% destruction and removal efficiencies of materials incinerated. The materials disposed of to the thermal oxidizers from the manufacturing of gemcitabine hydrochloride could include solvents, intermediates, unrecovered product and unreacted starting materials. Since these non-conventional liquid wastes will not be discharged to surface waters, they will not impact NPDES permit requirements.

The thermal oxidizers are predominantly horizontal, refractory-lined vessels. They feature a vortex burner section where primary wastes are introduced and an adjacent downstream section where secondary wastes are introduced. The rated capacities of the two units are 75 million BTUs per hour and 35 million BTUs per hour. The minimum combustion temperature of the 75 million BTU unit and the 35 million BTU unit are _____ and _____ respectively. Each thermal oxidizer's main burner has the capability to utilize auxiliary fuel or primary waste to raise the combustion chamber to the operating range and to maintain stable operating conditions. Each thermal oxidizer is equipped with a forced draft combustion air blower.

Both thermal oxidizers at Tippecanoe Laboratories are equipped for acid neutralization and removal of particulates and acidic gases from the incinerator exhaust in a gas cleaning system. The gas cleaning system for the 35 million BTU unit consists of a quench, a venturi scrubber, and a packed tower. The 75 million BTU unit has a quench, a separator, and a venturi scrubber. The quench section on each unit consists of a wetted approach downcomer and a carbon steel quench tank lined with acid resistant brick. On the larger unit, gases exhaust to a fiberglass reinforced plastic separator for water droplet removal.

Gases next flow to a wetted-approach variable throat venturi to remove particulates. The gases are then directed to the atmosphere through a fiberglass stack. On the smaller unit, the gases exiting the quench enter a wetted-approach, variable throat venturi. They are then directed through a packed tower and enter the atmosphere through a fiberglass stack. Carbon monoxide and oxygen are monitored in the stack of each unit to indicate proper operation of the combustion process.

b. Wastes from Formulating and Packaging

Formulation and packaging of Gemzar will be carried out at facilities of Eli Lilly and Company in Indiana (1555 Kentucky Ave., Indianapolis, IN 46221) and at Lilly France, S.A. (Rue du Colonel Lilly, 67640 Fegersheim, France). The areas where formulation occur will meet the standards for Good Manufacturing Practices. Manufacturing will include solution manufacturing, sterile filtration, filling, freeze drying, inspection/sorting and packaging. All room air will pass through HEPA filters (99.99% efficiency) and dust collectors, which will be packaged with solids, particulates, and dust for incineration at an approved facility.

After the filtration and filling equipment have been emptied, wash water from the rinsing of empty equipment and small amounts (approximately 0.2 liters) of manufactured solution from the formulations facility will be collected and discharged intermittently. In Indianapolis, this discharge will be sent to the municipal wastewater treatment facility under a permit issued by the Indianapolis Department of Public Works (DPW). In France the wash water will be discharged to the municipal wastewater facility in Strasbourg. These waters will primarily contain suspended solids which may be oxygen demanding materials. Small residues of gemcitabine (less than 24 grams) may exist in these waters.

Only a very small percentage (< 1%) of the daily discharge of wastewater from these municipal wastewater treatment facilities could be attributed directly to intermittent discharge of waste water from formulating and packaging of Gemzar. Both facilities

remove particulates and BOD before discharge to the White River in Indianapolis or to the Eel River in Strasbourg. If small residues of gemcitabine intermittently passed through the facilities, calculated concentrations of gemcitabine discharged in the effluent would be no higher than 0.04 µg/L. Concentrations would be well below this level after dilution by surface water.

Gemzar will be packaged in _____ The vials will be closed with stoppers, sealed with _____ and _____, and then placed in cartons. All packaging and labeling components will be confined to a restricted area. This packaging is necessary to protect products and customers by reducing the damage to the product during shipping. This packaging also enhances product stability, discourages tampering, and provides a surface for approved labeling.

Solid wastes generated from the formulating and packaging facilities generally will be cartons, paper, and plastic. Normal office wastes, boxes, and other non-hazardous trash will be sent to municipal disposal facilities. Any rejected material, plastic liners, gloves, hair covers, cartridge filters, HEPA filters, or other wastes that may contain hazardous materials will be incinerated at facilities in Indiana and France. In Indiana, these materials will be sent for incineration according to a Resource Conservation and Recovery Act permit issued by the U.S. EPA under facility identification number IND0702040348 to the following facility:

Eli Lilly and Company
State Road 63
Clinton, IN 47842

In France, these materials will be disposed of at the following industrial incinerator facility, which has two Prefectoral permits (approved May 14, 1985 and December 9, 1987) for industrial and chemical wastes:

c. Air Emissions

The manufacturing of gemcitabine hydrochloride involves 16 chemicals on the OSHA Air Contaminants List (Confidential Attachment 5). Air emissions from manufacturing, formulating, and packaging of gemcitabine hydrochloride were estimated by calculation. The volatile organic compounds that will be emitted were modeled with the air dispersion model SCREEN. The resulting ambient concentration for each compound was compared to the Acceptable Ambient Concentrations specified by IDEM or the Threshold Limit Values (TLVs) established by the American Conference of Governmental Industrial Hygienists (ACGIH) to insure that discharges from gemcitabine manufacturing processes will be below these acceptable levels.

B. INTRODUCTION OF SUBSTANCE FROM THE USE SITES

Gemzar will be used in hospitals and clinics, and can be used on an outpatient basis. Accordingly, any gemcitabine introduced into the environment will have the same general geographical distribution pattern as that which exists for human populations. Most of the population in the United States lives within 100 miles of some coastline.

Gemzar can be administered intravenously at a dose of 1000 mg/m^2 (about 1500 mg as the free base per adult) over 30 minutes once weekly for up to 7 weeks. This would be followed by a week without treatment. Additional treatment cycles of once per week for three weeks at the same dose, with a week off of treatment, could then be provided. Less than 2000 kg of gemcitabine hydrochloride is expected to be produced in the fifth year of its use on a world-wide basis. Less than 1000 kg of that total is expected to be used in the United States. If gemcitabine hydrochloride was administered for six months, a total dose of about 28.5 g of the free base could be used for an adult patient. At this total dose, about 35,000 people could be treated with gemcitabine hydrochloride each year ($1000 \text{ kg/year} + 0.0285 \text{ kg/person/year}$) in the United States. At this rate, the number of individuals

receiving gemcitabine would constitute a very small percentage (about 0.014%) of the human population in the United States.

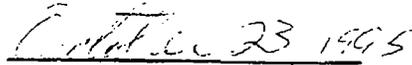
The pharmacokinetics and metabolism of gemcitabine have been studied (Allerhheiligen *et. al.*, 1993). Gemcitabine is metabolized intracellularly by deoxycytidine kinase and other nucleoside kinases to form the active materials gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine is also metabolized by cytidine deaminase to produce an inactive uridine derivative. Study results indicate that more than 92% of a gemcitabine dose is excreted within a week after administration. About 99% of the excreted material is found in the urine and less than 1% was found in feces. More than 90% of the residue found in urine is the inactive uridine derivative (2'-deoxy-2',2'-difluorouridine) of gemcitabine. Less than 10% of the residue excreted in urine is the active parent material. Inactive residues would be excreted along with small amounts of active material and would be discharged into municipal sewage treatment systems or into septic tanks.

LIST OF PREPARERS

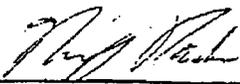
The following personnel of Eli Lilly and Company are responsible for the preparation of this Environmental Assessment.



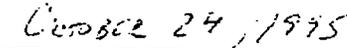
Roger D. Meyerhoff, Ph.D.
Head,
Environmental Science & Hazard Communications



Date



Neil J. Parke, M. A.
Senior Environmental Affairs Representative
Environmental Affairs



Date

CERTIFICATION

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.

Mark T. Owens

Mark T. Owens
Director
Occupational Health, Safety, and Environmental Affairs

10/26/95
Date

REFERENCES

ALLERHEILIGEN, S.R.B., CERIMELE, B.J., JOHNSON, R.J., HATCHER, B.L.
(1993). Summary of human pharmacokinetics of gemcitabine. Report of the Lilly
Laboratory for Clinical Research. 47 p.

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

/s/

Nancy Sager

7/13/02 07:32:43 PM

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into the electronic division file system (DFS). See
the document for original signatures and approval date.

Review Division Copy

SENSITIVE

REVIEW

OF

ABBREVIATED ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-509

GEMZAR® (GEMCITABINE HYDROCHLORIDE)

REVIEW DIVISION: HFD-150

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-004

DATE COMPLETED: May 30, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: October 1994
Consult #1
to HFD-004: April 27, 1995
Assigned: May 11, 1995
CSO: P. Dietze

2. Name of Applicant/Petitioner:

Eli Lilly and Company

Adequate.

3. Address:

Lilly Corporate Center
Indianapolis, Indiana 46285

Adequate.

4. Description of the proposed action:

a. Requested Approval:

NOTE: Based on the limited production and small target population for this product, due to its use for the treatment of a rare disease and infrequent use, an abbreviated EA is appropriate. Consequently, format items 7 through 11 and 15 are not required, and have not been reviewed.

Eli Lilly and Company is seeking approval for the manufacturing, formulating, packaging, and marketing of

Gemzar® (gemcitabine hydrochloride) for use in the treatment of adenocarcinoma of the pancreas. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis. Gemzar will be available in vials containing 200 mg or 1 g of gemcitabine (expressed as free base) in the form of a sterile _____ material. Gemzar may be administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks.

Adequate.

b. Need for Action:

Treatment of adenocarcinoma of the pancreas.

ADEQUATE

c. Production Locations:

i. Proprietary Intermediate(s):

None identified

ii. Drug Substance:

Production of gemcitabine hydrochloride will occur at the Eli Lilly and Company Tippecanoe production facilities near Lafayette, Indiana.

DEFICIENT. The complete address of the production facility must be provided.

iii. Finished Dosage Form:

Gemzar will be formulated and packaged at facilities of Eli Lilly and Company in Indianapolis, Indiana and at Lilly France, S.A. (Rue du Colonel Lilly, 67640 Fegersheim, France).

DEFICIENT. The complete address of the Indiana formulation and packaging facility must be provided.

d. Expected Locations of Use (Drug Product):

Gemzar will be administered in hospitals and on an outpatient basis throughout the United States.

Adequate.

e. Disposal Locations:

There is no discussion of disposal of off-specification drug substance or off-specification, expired, returned, or otherwise unused product.

DEFICIENT.

f. Types of environments present at and adjacent to production and disposal sites:

The manufacturing plant in Indiana is located in a temperate climate in a rural setting. The formulation and packaging plants in Indianapolis are in an urban setting. The facilities in France are in a temperate climate and a rural setting.

ADEQUATE

5. Identification of chemical substances that are the subject of the proposed action:

Drug Substance: Gemcitabine hydrochloride
Chemical Name: 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β -isomer).
CAS #: 122111-03-9
Molecular Weight: 299.66
Molecular Formula: $C_9H_{11}F_2N_3O_4 \cdot HCl$
Structural Formula: See page 429 of the EA.
Physical Descrip.: A white to off-white solid.
Additives: This is/will be adequately addressed as part of 6.a.

Impurities: Not identified, but _____ for impurities are stated. Since these are found at _____ they are not of concern and identification will not be requested.

Adequate.

6. Introduction of substances into the environment: For the site(s) of production:

a. Potential Emitted Substances:

Substances from manufacturing that are expected to be emitted to the atmosphere or wastewater treatment plant, or to be incinerated or disposed of off-site, are identified (kg/batch) in Confidential Attachment 2. Substances expected to be emitted as a result of formulating and packaging are not identified.

DEFICIENT. Substances expected to be emitted as a result of formulating and packaging must be identified. Quantities of emitted substances reported are based on per-batch; the EA does not clearly state the number of batches anticipated in the fifth year of production. Total annual production of the drug substance should be estimated for a five-year period.

b. Controls (Air, Liquid Effluent, Solid):

Tippecanoe facility

Releases into the environment of wastewater pollutants and liquid and solid wastes resulting from the production of gemcitabine hydrochloride will be controlled. Liquid process waste streams directly from the chemical synthesis of gemcitabine will either be recovered for reuse, treated by thermal oxidation, or treated by biological wastewater treatment. Solids and particulate filters will also be collected for incineration. Certain solids may also be recycled or disposed of at approved disposal facilities. Dilute wash waters from production processes will be thermally

oxidized or treated in biological wastewater treatment facilities.

For the Tippecanoe facility, a description was provided of the waste gases capture process, the chemical wastewater treatment system, and the primary waste and secondary waste liquid thermal oxidizers. Trace amounts of solvents may be released from the waste gases, depending on the efficiency of the scrubbers. Less than one percent of the daily discharge of wastewater will be attributed to gemcitabine hydrochloride manufacturing; the effluent, consistently maintained within the permit limits for pH, is discharged into the Wabash River. Sludges from the wastewater clarification system are thickened, dewatered, and digested before proper disposal. Two thermal oxidizers, designed to achieve 99.99% destruction and removal efficiencies, incinerate solvents, intermediates, unrecovered product and unreacted starting materials from the process.

DEFICIENT. The minimum permitted efficiency and typical operating efficiency of the waste gases scrubber system are not provided. Also, it is not clearly stated that solvent quantities released are expected to be within permitted levels. Similarly, there is no discussion of the facility's compliance with its NPDES permit (other than COD, BOD, and pH on page 434), and the anticipated impact that additions to the effluent resulting from the approval of gemcitabine hydrochloride manufacturing will have on permit compliance.

Indianapolis, Indiana and Fegersheim, France facilities

Formulation and packaging of Gemzar will be carried out at facilities of Eli Lilly and Company in Indianapolis, Indiana, and at Lilly France. Manufacturing room air will pass through HEPA filters and dust collectors, which will be packaged with solids, particulates, and dust for approved disposal.

Wash water from equipment rinsing and approximately 0.2 liters of manufactured solution will be collected and discharged. It is estimated that less than 24 grams of gemcitabine may exist in these waters. Suspended solids in the waters may be oxygen demanding materials. Predicted concentrations of gemcitabine discharged in the effluent would be no higher than 0.04 ug/L, and less after dilution with surface water.

Solid wastes generated from formulating and packaging facilities will be cartons, paper, and plastic. Any rejected material, plastic liners, gloves, hair covers, or cartridge filters will be disposed of at approved facilities (i.e., landfill or incinerator).

DEFICIENT. No information is provided concerning the efficiency of the HEPA filters or their disposal locations, or the locations of and appropriateness of landfilling or incinerating rejected gemcitabine material.

Manufacturing gemcitabine hydrochloride involves OSHA Air Contaminants List chemicals. Emissions from manufacturing, formulating, and packaging were estimated by calculation. The EA indicated that the air emissions were modeled with a dispersion model and compared to Acceptable Ambient Concentrations or the Threshold Limit Values.

DEFICIENT. The impact of these emissions on compliance is not provided.

c. **Compliance with Federal, State and Local Emission Requirements:**

Eli Lilly and Company will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at all production and formulation facilities.

DEFICIENT. There is no statement of current compliance with OSHA requirements.

A confirmation of intent to comply with environmental regulations governing the manufacture of Gemzar from the Fegersheim, France, facility is included in Appendix G.

Adequate.

d. **Effect of Approval on Compliance with Current Emissions Requirements:**

DEFICIENT. Briefly discuss the effect of approval on compliance with current emission requirements.

e. **Estimated Expected Emitted Concentration/Quantities:**

Total use of gemcitabine hydrochloride in a year in the United States is expected to be less than 1000 kg. About 35,000 people could be treated with gemcitabine hydrochloride each year, about 0.014% of the population of the United States.

DEFICIENT. Total annual production of the drug substance, based on a five-year market plan, should be provided.

7. **Fate of emitted substances in the environment:**

Due to the abbreviated EA format, this information is not required and was only briefly reviewed.

8. **Environmental effects of released substances:**

Due to the abbreviated EA format, this information is not required and was only briefly reviewed. It is clear from the information given that the drug substance would only be found in the aqueous compartment at several orders of magnitude less than toxic concentrations.

9. **Use of resources and energy:**

Due to the abbreviated EA format, this information is not required and was not reviewed.

10. Mitigation measures:

Due to the abbreviated EA format, this information is not required and was not reviewed.

11. Alternatives to the proposed action:

Due to the abbreviated EA format, this information is not required and was not reviewed.

12. List of preparers, & their qualifications (expertise, experience, professional disciplines) and consultants:

Roger D. Meyerhoff, Ph.D
Head, Environmental Science and Hazard Communications

Neil J. Parke, M.A.
Senior Environmental Affairs Representative, Environmental Affairs

Daniel E. Brock, M.S.
Toxicologist, Environmental Science and Hazard Communications

Jeffery A. Englehardt, D.V.M., Ph.D
Project Leader and Senior Research Scientist, Morphological Pathology

Adequate.

13. Certification:

Provided.

Adequate.

14. References:

Two references are cited.

Adequate.

15. Appendices:

Due to the abbreviated EA format, this information is not required and was not reviewed.

2 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

ATTACHMENT 1

SITE: Tippecanoe FUNCTION: production of gencitabine hydrochloride BASIS FOR EMISSIONS EST.: Not given					
Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements.	Effect of Action on Current Emission Requirements	
Air emission permits	79-04-90-0382 CP 157-1891 CP 157-2682 CP 157-2593 CP 157-1980	4/01/90* 8/16/98 N/A** N/A*** 7/13/97	Not provided Not provided Not provided Not provided Not provided	Unknown Unknown Unknown Unknown Unknown	
Municipal sewer system, aqueous waste streams					
NPDES	IN0002861	9/30/92*	Not provided	Unknown	
RCRA	IND006050967	4/30/93*	Not provided	Unknown	

Note: *A condition of the permit stipulates that the permit remains in force until the regulatory agency issues a new one, as long as timely application for a new permit is made before the expiration date. However, the company has not stated specifically that a timely application was made and that the permits are indeed in force.
 **Permit has no expiration date.
 ***This is a construction permit which has no expiration date. Upon completion of construction the operating permit will be validated and an expiration date will be issued.

ATTACHMENT 1

SITE: Indianapolis FUNCTION: formulation and packaging of Gemzar BASIS FOR EMISSIONS EST.: Not given				
Description	Permit #	Exp. Date/ Renewal Date	Applicable Emission Requirements.	Effect of Action on Current Emission Requirements
Air emission permits				
Municipal sewer system, aqueous waste streams	DPW 283001 DPW 283004	12/31/95 12/31/95	Not provided Not provided	Unknown Unknown

Endorsements:

HFD-004/NBSager *NBSager 6/15/95*

HFD-004/RAJerussi *Ra Jerussi 6/14/95*

CC: Original/PDietz copy to NDA 20-509/HFD-150
EA File 20509
CGood/HFD-102

File: 20509E00.rdc

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

CHEMISTRY REVIEW(S)

AUG 16 1995

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #20-509

CHEM.REVIEW #: 1

REVIEW DATE: August 11, 1995

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Pre-submission	22-Dec-94	27-Dec-94	06-Jan-95
Original	02-Feb-95	02-Feb-95	08-Feb-95

NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

DRUG PRODUCT NAME
Proprietary: Gemzar for Injection
Nonproprietary/USAN: Gemcitabine Hydrochloride for Injection
Code Name/#: LY264368
Chem.Type/Ther.Class: 1 P

PHARMACOL.CATEGORY/INDICATION: Pancreatic cancer

DOSAGE FORM: Lyophilized powder
STRENGTHS: 200 mg vial and 1 g vial
ROUTE OF ADMINISTRATION: IV
DISPENSED: Rx OTC

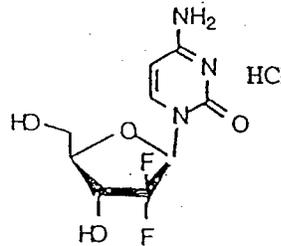
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

2'-deoxy-2',2'-difluorocytidine monohydrochloride
(β isomer)

Chemical Abstracts Number: 122111-03-9

M.W. 299.66g/mol

Molecular Formula: C₉H₁₁F₂N₃O₄·HCl



Gemcitabine Hydrochloride

SUPPORTING DOCUMENTS:

IND 29,653 Eli Lilly and Co.

Gemcitabine Hydrochloride.

DMF 4700 procedures. Eli Lilly and Co.

General operating

45 _ Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

71

FEB 8 1996

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #20-509 CHEM.REVIEW #: 2 REVIEW DATE: January 23, 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	09-Jan-96	11-Jan-96	23-Jan-96
Original	02-Feb-95	02-Feb-95	08-Feb-95
Pre-submission	22-Dec-94	27-Dec-94	06-Jan-95

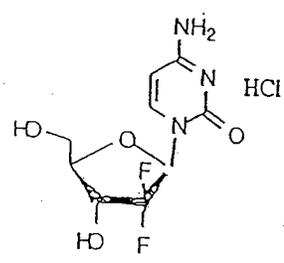
NAME & ADDRESS OF APPLICANT: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

DRUG PRODUCT NAME
Proprietary: Gemzar for Injection
Nonproprietary/USAN: Gemcitabine Hydrochloride for Injection
Code Name/#: LY264368
Chem.Type/Ther.Class: 1 P

PHARMACOL.CATEGORY/INDICATION: Pancreatic cancer

DOSAGE FORM: Lyophilized powder
STRENGTHS: 200 mg vial and 1 g vial
ROUTE OF ADMINISTRATION: IV
DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:
2'-deoxy-2',2'-difluorocytidine monohydrochloride
(β isomer)
Chemical Abstracts Number: 122111-03-9
M.W. 299.66g/mol
Molecular Formula: C₉H₁₁F₂N₃O₄·HCl



Gemcitabine Hydrochloride

SUPPORTING DOCUMENTS: None

CONSULTS:

<u>Consult</u>	<u>Status</u>	<u>Comments</u>
EA	Pending	Submitted on January 25, 1995. Initial review completed May 30, 1995. Responses to EA deficiencies submitted in this amendment were forwarded for consult on January 24, 1996.
Methods Validation	Hold	Will be initiated after all methods deficiencies have been addressed
Microbiology	Pending	To HFD-160 to evaluate the sterilization process for manufacture of the drug product. Submitted on January 25, 1995.

Review #1, dated 7/19/95, application not approvable for reasons of sterility assurance. Responses to micro deficiencies submitted in this amendment were forwarded for consult on January 24, 1996.

Biometrics	Pending	For analysis of stability data. Submitted July 2, 1995. Updated stability data submitted with this amendment were forwarded to biometrics for consult on January 24, 1996.
EER	Approved	Submitted on January 25, 1995. Indianapolis facility approved on July 7, 1995. The Fegersheim facility was found unacceptable has bween withdrawn as a manufacturing facility by the sponsor.
Trademark Review	Approved	Submitted on January 25, 1995.

REMARKS/COMMENTS:

The drug substance and drug product are manufactured by Eli Lilly. Several deficiencies were noted in our initial review of the NDA. There were serious deficiencies in the description of the synthesis of the drug substance. In addition there is insufficient stability data to support the manufacturing facility in France. These deficiencies were communicated to the sponsor by Agency facsimile dated September 28, 1995. This amendment is a response to the deficiencies cited in our original review of the NDA.

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-509 is not approvable from a chemistry manufacturing and controls perspective and a deficiency letter should be conveyed to the sponsor. The sponsor has addressed many of the deficiencies that existed in the original NDA. The sponsor has chosen a single synthetic route and the description of the synthetic route is described in much better detail. However, deficiencies are still present. The deficiencies will need to be addressed before the NDA can be approved.

See attached deficiency letter.

Paul E. Dietze 2/6/96

Paul E. Dietze, Ph.D.
Review Chemist

Eric Tolgyesi
2/8/96

cc:
Orig. NDA 20-509
HFD-150/Division File
HFD-150/PDietze
HFD-151/LMcCollum
HFD-150/ETolgyesi
R/D Init by:ETolgyesi

filename: n20509r2.000

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 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

APR 3 1996

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: #20-509

CHEM.REVIEW #: 3

REVIEW DATE: March 26, 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Amendment	04-Mar-96	04-Mar-96	07-Mar-96
Amendment	09-Jan-96	11-Jan-96	23-Jan-96
Original	02-Feb-95	02-Feb-95	08-Feb-95
Pre-submission	22-Dec-94	27-Dec-94	06-Jan-95

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

DRUG PRODUCT NAME

Proprietary:

Nonproprietary/USAN:

Code Name/#:

Chem.Type/Ther.Class:

Gemzar for Injection
Gemcitabine Hydrochloride for Injection
LY264368
1 P

PHARMACOL.CATEGORY/INDICATION:

Pancreatic cancer

DOSAGE FORM:

Lyophilized powder

STRENGTHS:

200 mg vial and 1 g vial

ROUTE OF ADMINISTRATION:

IV

DISPENSED:

X Rx OTC

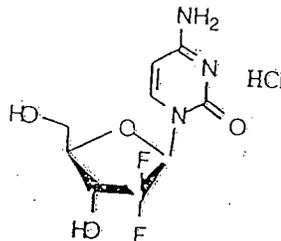
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

2'-deoxy-2',2'-difluorocytidine monohydrochloride
(β isomer)

Chemical Abstracts Number: 122111-03-9

M.W. 299.66g/mol

Molecular Formula: $C_9H_{11}F_2N_3O_4 \cdot HCl$



Gemcitabine Hydrochloride

SUPPORTING DOCUMENTS: None

CONSULTS:

Consult

Status

Comments

EA

Approved

Submitted on January 25, 1995. Initial review completed May 30, 1995. Responses to EA deficiencies submitted in this amendment were forwarded for consult on January 24, 1996. EA approved and FONSI prepared on 3/4/96

Methods Validation

Hold

Will be initiated after all methods deficiencies have been addressed

Microbiology

Pending

To HFD-160 to evaluate the sterilization

process for manufacture of the drug product. Submitted on January 25, 1995. Review #1, dated 7/19/95, application not approvable for reasons of sterility assurance. Responses to micro deficiencies submitted in this amendment were forwarded for consult on January 24, 1996. Review #2 indicated there were still micro deficiencies. These deficiencies were communicated to the sponsor by the CSO.

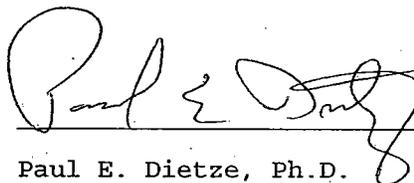
Biometrics	Approved	For analysis of stability data. Submitted July 2, 1995. Updated stability data submitted with this amendment were forwarded to biometrics for consult on January 24, 1996. Consult received 2/9/96 and the proposed expiry date for the drug product acceptable and supported by the statistical analysis. The statistical analysis also supported the proposed use time for reconstituted drug product. See also 2/14/96 amendment to Biometrics review.
EER	Approved	Submitted on January 25, 1995. Indianapolis facility approved on July 7, 1995. The Fegersheim facility was found unacceptable has been withdrawn as a manufacturing facility by the sponsor.
Trademark Review	Approved	Submitted on January 25, 1995.

REMARKS/COMMENTS:

The sponsor has adequately addressed all of the deficiencies in the NDA. There are no pending consults except for the microbiology consult. The EA and EER are acceptable.

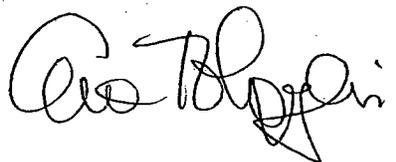
CONCLUSIONS & RECOMMENDATIONS:

From a chemistry manufacturing and controls perspective Eli Lilly's NDA # 20-509 for Gemzar should be approved once the microbiology deficiencies have been addressed and are found to be acceptable found to be acceptable by the consulting microbiologist.

 3/20/96
Paul E. Dietze, Ph.D.
Review Chemist

cc:
Orig. NDA 20-509
HFD-150/Division File
HFD-150/PDietze
HFD-151/LMcCollum
HFD-150/ETolgyesi
R/D Init by:ETolgyesi

filename: n20509r3.000

 4/3/96

19 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

MAR 5 1996

NDA#: 20-509
Applicant: Eli Lilly and Company
Name of Drug: Gemzar (Gemcitabine hydrochloride)
Indication: First line palliative therapy in patients with Carcinoma of the Pancreas
Documents Reviewed: Vols. 2.1, 2.35 - 2.71, 2.106 - 2.109 dated Feb. 1995
SAS Database
Medical Officer: Genny Schechter, M.D.

REVIEW SUMMARY

The Eli Lilly and Company has submitted five clinical studies, including a phase III single-blind, randomized, comparative trial (JHAY), and four phase II single-arm trials (JHAZ, JHAL, JHAL-extension, and E012) in support of an application for use of Gemzar for the treatment of pancreatic cancer.

This reviewer's own assessments and analyses are labeled as **Table, Figure, Analysis, Attachment, or Appendix** in the text or attached at the end of the review. The sponsor's tables and figures are attached after the review's Appendices. A report on the supplemental longitudinal analysis of trial JHAY by Dr. M. Takeuchi is included as an attachment.

1. For trial JHAY, the sponsor's results of the primary and secondary endpoints have been confirmed using the sponsor's database.
2. For trial JHAY, there was no statistical evidence indicating any imbalances at baseline with respect to the four baseline stratification factors (pain intensity, analgesic consumption, Karnofsky performance status, and investigator sites) used for the randomization (**Figure 1, Table 5, and Appendix 2**).
3. For trial JHAY, although the sponsor's 2x2 clinical benefit response (CBR) endpoint analysis resulted in statistically significantly different "positive" CBR rates (4.8% of 5-FU vs 23.8% of Gemzar) and "stable" CBR rates (58.7% of 5-FU and 39.7% of Gemzar), the "negative" CBR rates (36.5%) were identical for both the 5-FU and Gemzar arms. This reviewer's analysis indicated that the finding of a significantly higher CBR response rate in

the Gemzar arm depended on the classification of "positive" and "stable" CBR responders (see **Appendix 3**). This raises the question as to whether the sponsor's classification algorithm for CBR can adequately distinguish between "positive" and "stable" CBR patients.

4. In trial JHAY, the sponsor's 2x2 CBR endpoint analysis needs to be interpreted with caution due to the large differences in the distributions of patient discontinuation rates on the 5-FU and Gemzar arms (see **Appendix 4**).

5. The analyses of secondary endpoints (time to disease progression, time to treatment failures and survival), using the FDA MO's assessment of dates and censoring indicators, produced results similar to those provided by the sponsor (see **Tables 2-5**).

6. From this reviewer's exploratory survival analysis, the survival advantage in the Gemzar group (mortality risk ratio) was homogeneous when patients were stratified by either pain intensity, or analgesic consumption. Homogeneity did not hold when patients were stratified by Karnofsky performance status (KPS), sponsor assessed baseline stage, or the FDA MO assessed clinical stage. Results with heterogeneous strata indicated that the survival advantage in the Gemzar arm was confined to patients with KPS greater than 70, with baseline stage 4, and without baseline liver metastasis (see **Tables 7-12**).

BACKGROUND

The Eli Lilly and Company has submitted a phase III randomized controlled study (JHAY), a phase II single agent study (JHAZ), and two other single agent studies (JHAL, E012) in support of an application for use of Gemcitabine hydrochloride (Gemzar) for the first line palliative therapy in patients with carcinoma of the pancreas.

TRIAL JHAY

1. STUDY DESCRIPTION

The JHAY trial was a multicenter (19), single-blind, randomized, Phase III, controlled study. A total of 160 patients with advanced or metastatic pancreatic cancer were recruited. Of those, 34 patients were not randomized (17 no longer eligible, 10 inadequate pain stabilization, 4 concurrent medical problems, and 3 patient's choice). The remaining patients were randomized to either the Gemzar (n=63) or the 5-Fluorouracil (5-FU) (n=63) arms. The enrollment period was between July 22, 1992 and March 23, 1994 (20 months). The study was ongoing as of the data cutoff date Sep. 23, 1994 (6 months minimum follow-up). Prior to randomization, each patient participated in a 'lead-in period' which may have lasted from 2 to 7 days. A patient could not be randomized to a treatment arm if his or her analgesic consumption and pain intensity were not stabilized during this period.

The primary objective was "to establish an advantage in clinical benefit of Gemzar over 5-FU as measured by **significant improvement in pain, performance status, or weight change**". The secondary objectives were "to compare the treatment arms with respect to time to progressive disease, survival, objective tumor response rates, duration of clinical-benefit response, and univariate assessments of the primary variables, and to assess differences in the population pharmacokinetics in patients treated with Gemzar and 5-FU".

Gemzar was administered at a dose of 1000mg/m² for 30 minutes once weekly for up to 7 weeks, followed by a week of rest, then once weekly for 3 weeks out of every 4 weeks. 5-FU was administered at a dose of 600mg/m² for 30 minutes once weekly (see sponsor Tables 4 and 5 in Vol. 2.35). All patients were to remain enrolled in the study until there was evidence of further disease progression or until the patient was discontinued. For those patients who achieved a complete tumor response, up to 8 additional cycles were to be given before treatment was discontinued.

Randomization was stratified on four prognostic factors: pain intensity (PI), analgesic consumption (AC), Karnofsky

performance status (KPS), and investigator site (IS). The Pocock and Simon dynamic allocation algorithm (1975) was used, with a randomization probability parameter of 0.75. The dichotomy of each factor, low vs high, was initially created based on a 50-50 split. These cut-off values were changed after discussion with FDA, viz., for PI, from 30 morphine-equivalents mg/day to 20, for AC, from 60 to 10 morphine-equivalent mg/day, and for KPS, from 70 to 80.

The protocol definition of a clinical benefit responder (CBR) can be found in the Appendix 1. A summary of CBR follows. PI, AC, and KPS were the primary measures of clinical benefit, and weight was secondary. For a given individual, the categorization of weekly mean PI and AC jointly determined an overall weekly pain related score of positive, negative, or stable. Further, the categorization of overall weekly pain score and KPS jointly determined an overall CBR of a responder, nonresponder, or stable patient. If the status of CBR was classified as stable from the primary clinical benefit response measure, the patient was then further evaluated based on change in body weight (positive or nonpositive). If the weight change was positive (7% increase from baseline), then the patient was a CBR responder; otherwise, he or she was classified a CBR nonresponder.

The secondary efficacy endpoints, survival and time to disease progression (TTP), were measured from the time of randomization. The time to treatment failure (TTF) was defined as the time from randomization until the time the patient discontinued from the study treatment. The objective tumor response rate (OTR) is also a secondary endpoint. The duration of CBR in weeks was measured as the largest number of consecutive weeks that contained no back-to-back nonpositive weekly scores. If only one component is positive, the duration is the duration of the positive classification for that component. If multiple components are positive, the duration is the largest number of consecutive weeks that are primary positive weeks for at least one of the positive components.

2. OVERVIEW OF SPONSOR'S STUDY RESULTS AND REVIEWER'S ANALYSES OF SECONDARY ENDPOINTS BASED ON THE FDA MO'S ASSESSMENT

One hundred and sixty patients with pancreatic cancer were entered into the study. Thirty-four patients were not qualified for randomization (see sponsor table 7, Vol. 2.35). The intent-to-treat (ITT) analyses were based on 126 patients, 63 patients per arm. The qualified study patients included 54% males and 46% females on each arm. Patient ages ranged from 37 to 79 years with a median age of 62 years for Gemzar and 61 years for 5-FU patients. The majority of the patients were Caucasian (92% on the Gemzar arm and 84% on the 5-FU arm). All patients were chemo-naive. Three patients on the Gemzar arm received prior

radiotherapy. With the exception of one Gemzar patient, previous surgery or diagnostic procedures were undertaken for all qualified patients. The sponsor's baseline disease characteristics can be found in Table 1 of Vol. 2.35.

Primary Efficacy Endpoints - CBR

- ◆ The CBR rates of Gemzar (23.8%, 15/63) and 5-FU (4.8%, 3/63) were statistically significantly different (p=.002, Chi-square test, see sponsor Table 8 of Vol. 2.35).

Secondary Efficacy Endpoints - OTR, TTP, TTF, SURV

- ◆ The results of analyses on objective tumor response rate (OTR), time to disease progression (TTP), time to treatment failure (TTF), and survival time according to the sponsor's assessment and the FDA MO's assessment were summarized in the following TABLES.

Objective Tumor Response Rate (OTR)

The FDA MO determined that there were two responders each on the Gemzar and 5-FU arms (response rate 3.2%, p=1.00). The sponsor had 3 responders in the Gemzar arm and 0 in the 5-FU arm (4.8% for Gemzar vs 0% for 5-FU, p=.080) These results are summarized in Table 1 from reviewer's analyses.

Table 1 - Objective Tumor Response Rate

ARM	SPONSOR ASSESSMENT		FDA MO ASSESSMENT	
	5-FU	GEMZAR	5-FU	GEMZAR
OTR (95%CI)	0% (0/63) NA	4.8% (3/63) (0%-10.2%)	3.2% (2/63) (0%-7.6%)	3.2% (2/63) (0%-7.6%)
P-VALUE	.080		1.00	

Time to Disease Progression (TTP)

TTP was defined by the sponsor as the time from randomization until the time that the patient is classified as having progressive disease or until the time that the patient discontinued from the study treatment whichever is earlier. The conventional definition of TTP would consider patients who withdrew from the trial earlier than their disease progression as censored at the time of withdrawal rather than an event for disease progression. The results of analysis using the FDA MO's assessment were similar to those of the sponsor. The estimated median TTP was .96 months for 5-FU (.92 months, sponsor result) and 2.15 months for Gemzar (2.33 months, sponsor's result); these results were in favor of Gemzar (p=.005, FDA assessment, and p=.0002, sponsor assessment), as shown in Table 2 below.

Table 2 - Time to Disease Progression

ARM	SPONSOR ASSESSMENT		FDA MO ASSESSMENT	
	5-FU	GEMZAR	5-FU	GEMZAR
MEDIAN(mon) (95%CI)	.92 (.92-1.61)	2.33 (1.94-3.72)	.96 (.86-1.88)	2.15 (1.85-3.67)
RANGE	0-11.97+	0-13.32	0-12.01+	0-9.52
CENSORING	19%(12/63)	30%(19/63)	19%(12/63)*	18%(11/63)*
RISK-RATIO (G:F,95%CI)			.543 (.351-.841)	
LOG-RANK	.0002		.005	

* There were 18 patients who were 'NE' (non evaluable) for tumor response, 12 from Gemzar arm and 6 from 5-FU arm.

Time to Treatment Failure (TTF)

Table 3 - Time to Treatment Failure

ARM	SPONSOR ASSESSMENT		FDA MO ASSESSMENT	
	5-FU	GEMZAR	5-FU	GEMZAR
MEDIAN (95%CI)	.92 (.89-1.58)	2.04 (1.81-3.06)	.89 (.83-1.02)	1.85 (1.32-2.35)
RANGE	0-11.97+	0-13.32	0-12.0+	0-9.52
CENSORING	0%(0/63)	1.6%(1/63)	0%(0/63)	1.6%(1/63)
RISK-RATIO (G:F,95%CI)			.570 (.397-.819)	
LOG-RANK	.0004		.0018	

The sponsor defined the TTF as the time from randomization until the time that the patient discontinued from the study treatment. Treatment failure events as defined by the FDA MO were disease progression, toxicity, or death whichever occurred first. Analyses results of the sponsor and this reviewer are shown in **Table 3**. The estimated median TTF was shorter (by .03 mon. for 5-FU and by 0.19 mon. for Gemzar) using the FDA MO's assessment. TTF was significantly longer (by 0.96 months) for Gemzar (p=.0018, FDA MO; p=.0004, sponsor, log-rank test). The estimated risk ratio of Gemzar to 5-FU was .57 with 95% CI of .40 to .82.

Survival

For survival analysis, two patients (patients 219-3321: 6/1/94 and 219-3322: 5/23/94) were dead on the 5-FU arm based on

the FDA MO's determination, but they were censored at the study cutoff (9/23/94) by the sponsor. With this discrepancy, the estimated median survival was a little longer (by 0.07 mon.) for the Gemzar arm and a little shorter (by 0.15 mon.) for the 5-FU arm using the FDA MO's assessment. The Gemzar arm had a longer median survival (by 1.46 mon.) than the 5-FU arm (p=.0008, FDA MO; p=.0024, sponsor, log-rank test, see Table 4).

Table 4 - Survival

ARM	SPONSOR ASSESSMENT		FDA MO ASSESSMENT	
	5-FU	GEMZAR	5-FU	GEMZAR
MEDIAN(mon) (95%CI)	4.41 (3.39-5.19)	5.65 (4.70-6.87)	4.26 (3.24-5.16)	5.72 (4.83-6.94)
RANGE	0-15.09+	0-18.64	0-15.21+	0-18.78
CENSORING	4.8%(3/63)	12.7%(8/63)	1.6%(1/63)	12.7%(8/63)
6-MON. PROB	31%	46%	27%	44%
9-MON. PROB	6%	24%	3.2%	22%
1-YR PROB	2%	18%	1.6%	15%
RISK-RATIO (G:F,95%CI)			.531 (.364-.772)	
LOG-RANK	.0024		.0008	

Except for minor numerical differences, longer median time to disease progression (by 1.19 months, p=.005), longer median time to treatment failures (by 0.96 months, p=.002), and longer median survival (by 1.46 months, p=.008) were all in favor of Gemzar (based on the FDA MO's assessment on all the dates for time to event calculation, including date of randomization, date of disease progression, date of off-study, and date of death).

3. REVIEWER'S EVALUATION AND COMMENTS

3.1 Primary efficacy endpoints

Randomization was stratified on the following four prognostic factors: PI, AC, KPS, and investigator site. The baseline distribution of each factor is displayed in Figure 1. There was no statistical evidence indicating imbalance between Gemzar and 5-FU with respect to PI (p=.886), AC (p=.543), and KPS (p=.863) using the nonparametric two sample Wilcoxon test. As shown in Table 5 (see Appendix 2.), there was no apparent treatment imbalance by investigator sites.

The robustness of the CBR classification was investigated by this reviewer (please refer to **Appendix 3** for detail). From the reviewer's analyses using the six possible definitions at the overall weekly pain score level and the overall CBR response analyses, the treatment effect was differentiated when a CBR responder requires an individual to have just one component being positive with the other two components being stable or to have two components being positive with the other component being stable. Such treatment effect can not be concluded when a CBR responder requires an individual to have all three components being positive.

Although the observed CBR rate on Gemzar (23.8%) was statistically significantly better than that of 5-FU (4.8%), the impact of the extremely high and differential dropouts (see **Table 6**) between the two arms cannot be overlooked.

Table 6 Patients' Treatment Withdrawal Over Time (JHAY)

Dropouts by	Gemzar (N=63)	5-FU (n=63)
4 weeks	18%	38%
8 weeks	38%	68%
12 weeks	60%	81%
16 weeks	68%	86%

Assessment of the Impact of Dropouts on CBR

The following two approaches were used to assess the impact of the dropouts. The first approach treated CBR as a composite endpoint and adjusted patients' completion and discontinuation information for CBR rate and the second approach, done by Dr. M. Takeuchi, used longitudinal data for each component, PI, AC, and KPS to assess the CBR response profile individually.

Analysis of CBR based on patients' treatment completion status by 12-week and discontinuation reasons

The impact of dropouts on the sponsor's CBR analysis was evaluated. This reviewer reanalyzed CBR data in the following ways (please refer to **Appendix 4** for detail):

- Analysis based on retrospective stratification of the CBR responders by their treatment time on trial

Analysis 1 - Distribution of Clinical Benefit Response

COMPLETERS (stayed on study 12 wk or more)				NON-COMPLETERS (stayed on study less than 12 wk)			
	NR	R	TOT		NR	R	TOT
5-FU	9	2 (18%)	11	5-FU	51	1 (2%)	52
GEM	9	12 (57%)	21	GEM	39	3 (7%)	42

Cochran-Mantel-Haenszel, $p=.016$ (retrospectively stratified)

From **Analysis 1**, the CBR response rate was still higher in the Gemzar arm. For the completers, the CBR response rate was 57% on the Gemzar arm and 18% on the 5-FU arm; for the non-completers, 7% on the Gemzar arm and 2% on the 5-FU arm. The difference in the CBR response rate between the treatment arms over the two retrospective strata was statistically significant (Cochran-Mantel-Haenszel, $p=.016$).

- Analysis based on the reasons for discontinuation assessed by the FDA MO.

Through consultation, the reasons for discontinuation were provided by the FDA MO. In this reviewer's analysis, they were ranked from the best (complete tumor response) to the worst (death). **Analysis 2** used detailed ranking order of the reasons for discontinuation and the **Analysis 3** used the ranking order as complete tumor response, stable disease, adverse event/toxicity, lack of efficacy (clinical or objective progression), and death.

If the ranking is adequate, the Wilcoxon rank sum test indicates that a larger proportion of the Gemzar patients discontinued the treatment due to adverse events/toxicity (28.6%), compared to the 5-FU arm (11.3%) and the Gemzar arm had a smaller proportion of patients that discontinued treatment due to lack of efficacy/death (68.3%) than 5-FU arm (87.1%).

- Analysis incorporating reasons of discontinuation into CBR response rate

Using the protocol defined schema of 12 weeks to define the completers and non-completers, the distributions of the CBR responders and non-responders based on the reasons for discontinuation were explored.

There was a concern that non-completer non-responders might not have the opportunity to respond because they did not stay in the trial long enough. Their impact may be assessed by ranking the reasons for discontinuation along with responder completers, non-completers. **Analyses 4 and 5** present such analyses. Patients were classified as follows. Completers or responders were

classified into 'R' (complete response by week 12), 'BR' (might not complete 4 consecutive weeks CBR response by week 12), 'LR' (not yet responded by week 12), and 'NR' (completer non-responders). Non-completer non-responders were classified as 'AE' (adverse event), 'TO' (toxicity), 'LOE-SD' (lack of efficacy due to stable disease), 'CP' (clinical progression), 'LOE-PD' (lack of efficacy due to objective progression), and 'DE' (death), based on discontinuation reasons.

Since it is not entirely clear how one should rank the completer nonresponders ('NR') vs the non-completer non-responders, two alternative ways of ranking the 'NR' group were explored. In the first analysis, the 'NR' group was ranked better than non-completer non-responders (see **Analysis 4**). In the second analysis, the 'NR' group was not distinguished from the non-completer non-responder group and was reclassified based on the reasons of discontinuation (see **Analysis 5**).

Gould's approach (1980, Biometrics, 36, p.721-727) was applied to assess the potential impact of discontinuation on the CBR response distribution. The Wilcoxon rank sum test (Gould's approach) indicated that the Gemzar patients had a higher CBR response rate or tended to discontinue treatment for less severe reasons than the 5-FU patients (see **Analyses 4 and 5**). A potential concern about the adequacy of the ranking scheme arises from the question of whether clinical progression is more severe than lack-of-efficacy due to stable disease. A sensitivity analysis was performed by switching the order of CP and LOE-SD. Statistical significance still holds using the Wilcoxon rank sum test ($p=.004$ for rank method 1, and $p=.002$ for rank method 2).

In summary, there seem to have a numerical trend of CBR benefit, in terms of higher CBR rates, higher adverse events/toxicity, and lower disease progression, from Gemzar or a statistically significant treatment effect after adjustments for the ranked discontinuation distribution, the completer status, or combination of the two.

Analysis of CBR based on longitudinal data of each component

The following is a summary of Dr. M. Takeuchi's memorandum of statistical consultation dated 12/11/95 (see **Attachment**).

As pointed out by Dr. Takeuchi (section 2, page 2 and Figure 2 of the Memorandum), the patient attrition rates were high in both treatment arms, but appear to be higher in the 5-FU arm than in the Gemzar arm. In view of the fact that the primary endpoint, CBR, is defined in terms of weekly average scores of three different components in a complicated scheme, the observed differential dropout rates over time may confound the efficacy assessment of the overall clinical benefit response. In order to

assess the impact of the differential dropout rates over time, a reasonable approach is to analyze the clinical benefit response over time as longitudinal data. In this case, since the clinical benefit response is defined in terms of essentially three individual components, it is necessary to analyze the individual components over time.

Dr. Takeuchi analyzed the individual components over time and assessed the impact of the differential dropout rates on these components. He demonstrated that patients did not drop out at random and relative to each component, there were significant differences in the treatment response between patients who completed the trial and patients who dropped out early relative to each component.

Because of these differences, it is necessary to model the response over time separately for the dropouts and the completers. More specifically, the PI analysis suggested that Gemzar reduced PI over a period up to 12 weeks in both dropouts and completers, while for 5-FU patients the observed effects depended on classification; no PI reduction was noted for dropouts, but in completers the effect was similar to Gemzar (see Summary 1B). The AC analysis indicated that Gemzar dropouts had fairly constant AC, but 5-FU dropouts had a noticeable increase. For completers, however, the AC time trend (see Summary 2B) for Gemzar patients was quadratic (concave up), where no apparent change over time in AC was discerned for 5-FU completers. Finally, the KPS analysis revealed KPS decreasing at a constant rate for dropouts in both treatment arms, but the rates were different. For KPS of completers, Gemzar was found to have a quadratic (concave down) time profile (see Summary 3B), while that for 5-FU was found to randomly fluctuate around baseline values.

In summary, as stated in Dr. Takeuchi memorandum, 'the attrition rates in both treatment groups were extremely high, and the sample sizes in both arms were small. Therefore, all analyses of clinical benefit response and its components have the potential to be biased. Results, therefore, should be interpreted cautiously'. He concluded that 'by the robust results obtained from the longitudinal analyses, it is concluded that the beneficial aspects in each of the three components of the clinical benefit response endpoint point toward a positive effect for Gemcitabine'.

3.2 Secondary efficacy endpoints

3.2.1 Survival comparison stratified by weekly pain intensity, weekly analgesic consumption, or Karnofsky performance status

Table 7 summarizes the results of the log-rank test stratified on weekly pain intensity. Data did not indicate any

heterogeneity in the mortality risk ratio of Gemzar to 5-FU (p=.956). The estimated risk ratio was .57 with 95% C.I. between 0.39 and 0.85 (p=.005, stratified log-rank test).

Table 7 - Survival Comparison Between Gemzar and 5-FU for Pain Intensity Component of the Primary Endpoint**

Weekly PAIN	5-FU(n=63)		GEMZAR(n=63)		treatment effect
	Median 95%CI, days	Censoring(n)	Median 95%CI, days	Censoring(n)	
0-20	147(79-189)	4%(24)	190(98-243)	16%(19)	Log-rank p=.005 Risk ratio (95%CI) .57(.39-.85)
20-30	107(98-188)	0%(9)	156(89-210)	7%(14)	
30-40	54(27-154)	0%(11)	188(163-385)	8%(12)	
40-50	131(50-152)	0%(10)	238(163-301)	11%(9)	Homogeneity across strata p=.956
>=50	159(50-198)	0%(9)	137(79-159)	22%(9)	

**all dates for time to event calculation were based on FDA MO's assessment

Table 8 of this reviewer gives the results of the log-rank test stratified on weekly analgesic consumption. The mortality risk ratio did not indicate any heterogeneity between Gemzar vs 5-FU (p=.162). The stratified risk ratio was .48 with 95% C.I. between 0.33 and 0.72 (p=.0002, stratified log-rank test).

Table 8 - Survival Comparison Between Gemzar and 5-FU for Analgesic Consumption Component of the Primary Endpoint**

Wk-AC	5-FU(n=63)		GEMZAR(n=63)		treatment effect
	Median 95%CI, days	Censoring(n)	Median 95%, days	Censoring(n)	
0-10	232(98-.)	33%(3)	109(90-.)	33%(3)	Log-rank p=.0002 Risk ratio (95%CI) .48(.33-.72)
10-50	150(96-214)	0%(14)	222(187-538)	25%(16)	
50-100	126(50-159)	0%(19)	163(92-190)	10%(21)	Homogeneity across strata p=.162
100-200	130(63-156)	0%(16)	146(83-175)	0%(17)	
>=200	86(39-198)	0%(11)	236(203-270)	17%(6)	

** all dates for time to event calculation were based on FDA MO's assessment

Table 9 - Survival Comparison Between Gemzar and 5-FU for Karnofsky Performance Status Component of Primary Endpoint**

KPS	5-FU(n=62)*		GEMZAR(n=63)		Homogeneity p=.004
	Median (95%CI)	Censoring(n)	Median (95%CI)	Censoring(n)	Risk ratio(95%)
50	108(-)	0%(1)	50(45-54)	0%(2)	-
60	46(23-198)	0%(8)	86(25-109)	0%(9)	.94(.35-2.57)
70	136(104-163)	3%(34)	190(163-234)	15%(33)	.49(.29-.83)
80	159(79-214)	0%(13)	146(61-538)	18%(11)	.45(.17-1.22)
90	72(27-129)	0%(6)	231(131-265)	13%(8)	.11(.02-.57)

* one patient has KPS missing.

** all dates for time to event calculation were based on FDA MO's assessment

Based on the KPS stratification, the data indicated a possible heterogeneity on the mortality risk ratio between Gemzar vs 5-FU (p=.004). The risk ratios by the KPS score, as given in **Table 9**, suggest that as a patient's KPS increases, the risk ratio of Gemzar to 5-FU tends to decrease.

3.2.2 Survival comparison stratified by baseline stage, liver metastasis

The potential impact of the patient's disease status (in terms of clinical stage, baseline stage defined by the sponsor, and baseline liver metastasis status) on the survival time were assessed by this reviewer.

In **Table 10**, the risk ratio of Gemzar to 5-FU differed significantly between the patients who had liver metastasis at baseline and those who did not (p=.0001). The risk ratio was .47 (95% CI .26 to .84) in patients without baseline liver metastasis and .71 (95% CI .43-1.15) in patients with baseline liver metastasis. The significant survival benefit of Gemzar seemed to be mostly in the patients without baseline liver metastasis (8.4 weeks longer - without baseline liver metastasis and 1.0 weeks longer - with baseline liver metastasis).

Table 10 - Survival Comparison Between Gemzar and 5-FU (JHAY Study) by Baseline Liver Metastasis**

LIVER MET	5-FU (n=63)		GEMZAR (n=63)		Homogeneity p=.0001
	Median 95%CI, days	Censoring(n)	Median 95%CI, days	Censoring(n)	risk ratio 95%CI
NO	163 (129-211)	4% (25)	222 (173-270)	22% (32)	.47 (.26-.84)
YES	104 (63-133)	0% (38)	112 (83-150)	3% (31)	.71 (.43-1.15)

*all dates for time to event calculation were based on the FDA MO's assessment

Based on stratification by baseline stage, the data seemed to indicate that the mortality risk ratio differed either using the FDA MO's assessment of baseline clinical stage (p=.001; see Table 11) or using the sponsor's baseline stage (p=.003; see Table 12). The point estimate of the mortality risk was lower for the Gemzar arm than the 5-FU arm in all strata (some strata with small patient sizes need to be interpreted with caution).

Table 11 - Survival Comparison Between Gemzar and 5-fu (JHAY Study) by Baseline Stage**

FDA-MO STAGE	5-FU (n=62) *		GEMZAR (n=63)		Homogeneity p=.001
	Median 95%, days	Censoring(n)	Median 95%, days	Censoring(n)	risk ratio 95%CI
2	205 (129-236)	7% (14)	215 (173-385)	25% (16)	.63 (.28-1.40)
3	153 (50-195)	0% (4)	436 (159-538)	25% (4)	.15 (.02-1.41)
4	106 (54-135)	0% (44)	144 (98-201)	7% (43)	.55 (.35-.86)

* one patient had 'diagnosis in question'

** all dates for time to event calculation were based on FDA MO's assessment

Table 12 - Survival Comparison Between Gemzar and 5-fu (JHAY Study) by Baseline Stage**

SPONSOR STAGE	5-FU (n=63)		GEMZAR (n=63)		Homogeneity p=.003
	Median 95%, days	Censoring(n)	Median 95%, days	Censoring(n)	risk ratio 95%CI
2	198 (41-.)	20% (5)	243 (175-568)	22% (9)	.67 (.19-2.37)
3	156 (135-195)	0% (10)	187 (152-538)	22% (9)	.49 (.17-1.46)
4	104 (54-137)	0% (48)	150 (112-201)	9% (45)	.54 (.35-.83)

** all dates for time to event calculation were based on FDA MO's assessment

TRIAL JHAZ

1. STUDY DESCRIPTION

Trial JHAZ was a multicenter (17), single-arm, open-label study of Gemzar in patients (n=74) with advanced pancreatic cancer whose disease progressed on 5-FU either as a single agent or in combination with immunomodulators or biochemical modulators. The study enrollment was from Aug. 13, 1992 to March 8, 1994 with a study cutoff of Sept. 8, 1994. 11 patients did not receive the study drug. The original sample size calculation of n=56 was based on a 92% chance of detecting a CBR rate of 25% and a 5% type I error rate of concluding that a compound with a true CBR rate of 10% is effective. The amended protocol allowed accrual of up to 10 additional patients to anticipate protocol violations. The patient's baseline disease characteristics were summarized in sponsor's Table 1, Vol. 2.47.

Gemzar was administered at a dose of 1000mg/m² for 30 minutes once weekly for up to 7 weeks followed by a week of rest, then once weekly for 3 weeks out of every 4 weeks. This schedule was the same for the Gemzar arm in the JHAY trial. The primary objective of this trial was to determine the clinical benefit response rate to Gemzar measured by significant improvement in pain, performance status, or weight change. Secondary objectives were to assess TTP, survival, objective tumor response rates, and duration of CBR.

2. OVERVIEW OF SPONSOR'S STUDY RESULTS AND REVIEWER'S ANALYSES OF SECONDARY ENDPOINTS BASED ON THE FDA MO'S ASSESSMENT

In trial JHAZ, seventy-four patients with advanced pancreatic cancer whose disease progressed on 5-FU were entered into the study. Eleven patients were ineligible. The ITT analyses were based on 63 patients. The study population included 51% males and 49% females. Patient ages ranged from 33 to 77 years with a median age of 62 years. The majority of the patients were Caucasian (91%). The sponsor's summary of baseline disease characteristics can be found in Table 6.2 of Vol. 2.47.

Primary Efficacy Endpoints - CBR

- ◆ The CBR rate was 27% (17/63) for Gemzar (see sponsor Table 3 of Vol. 2.47).
- ◆ 11 out of 74 patients were excluded from the study (see sponsor Table 1 of Vol. 2.47). Using the FDA MO's assessment, 8 out of 71 patients were ineligible. The analysis was based on the remaining 63 patients, 9 of the 63 patients were non-evaluable for tumor response and disease progression.

Based on the FDA MO's assessment, the secondary endpoint results are as follows. The objective tumor response rate was 4.8% (3/63) with 95% CI of 0% to 10%. The median TTP was 61 days (95% CI: 56-85 days; range: 0 - 531 days) with censoring rate of 13% (7/54). The median TTF was 57 days (95% CI: 36-64 days; range: 0-531 days) with censoring rate of 1.6%(1/63). The median survival was 119 days (95% CI: 96-149 days; range: 0-531 days) with censoring rate of 7.9% (5/63).

3. REVIEWER'S EVALUATION AND COMMENTS

Table 13 - The Efficacy Results From the Sponsor and the FDA

	SPONSOR RESULTS	FDA RESULTS
Objective tumor resp	10.5%(6/57)	4.8%(3/63) 95%CI: 0%-10%
Median TTP	2.5 months	2.0 months censoring:13%(n=54)*
Median TTF	2.1 months	1.9 months censoring:1.6%(n=63)
Median survival	3.8 months**	3.9 months censoring: 7.9% (n=63)

* 9 patients were 'NE' for the TTP

** qualified patients (63 out of 74 patients were treated with Gemzar)

The efficacy results summary of this phase II, single arm trial are shown above in Table 13. Except for objective tumor response rate, the estimated median TTP, TTF and survival were similar for sponsor and FDA analyses.

TRIAL JHAL

1. STUDY DESCRIPTION

A multicenter (3, all in US), open-label, nonrandomized, single arm study. The study was designed to accrue up to 35 qualified patients, using a 3-stage design with the objective of minimizing the expected number of patients treated in the event that Gemzar therapy proved either very disappointing or very successful. Study enrollment was from Jan. 23, 1990 to Nov. 15, 1990 (a little less than 10 months). The study completion date was Feb. 4, 1992.

Gemzar was administered intravenously at a dose of 800 mg/m² for 30 minutes once a week for a consecutive 3-week period, followed by a fourth week of rest. The duration of each treatment

cycle was 28 days. The primary endpoints were best overall tumor response, Kaplan-Meier estimates of the time (on study) to events for response parameters, and sites of disease progression. The secondary endpoints were performance status, weight change, and analgesic consumption.

2. OVERVIEW OF SPONSOR'S STUDY RESULTS AND REVIEWER'S ANALYSES OF SECONDARY ENDPOINTS BASED ON THE FDA MO'S ASSESSMENT

◆ In trial JHAL, four out of forty-five patients were not qualified for the study (see sponsor Table 5.2 of Vol. 2.51). Using the FDA MO's assessment, 9 patients were excluded from a total of 53 patients, the remaining 44 patients (6 of them were non-evaluable for tumor response) were the basis for the analyses. The following results were obtained using the FDA MO's assessment. The objective tumor response rate was 4.5% (2/44) with 95% CI of 0% to 11%. For time to event analyses, patient# 210-1324 had date of first treatment later than the study completion date (Feb. 4, 1992) and was excluded from the analyses. The median TTP was 85 days (95% CI: 56-105 days; range: 0-244+ days) with censoring rate of 10.8% (4/37). The median TTF was 57 days (95% CI: 29-85 days; range 0-244 days) with censoring rate of 0% (0/43). The median survival was 103 days (95% CI: 49-128 days; range: 0 - 275 days) with censoring rate of 14% (6/43).

TRIAL E012

1. STUDY DESCRIPTION

A multicenter (3, all in Europe), open-label nonrandomized phase II efficacy study in patients (n=34) with pancreatic cancer. The study enrollment period was about 13 months (between Sept. 26, 1990 and Oct. 24, 1992) and the study cutoff date was Dec. 24, 1992. The study's primary objective was to determine the tumor response rate to Gemzar given weekly (at a starting dose of 800 mg/m²) for 3 weeks followed by 1 week of rest (one cycle) to chemo-naïve patients with advanced and/or metastatic pancreatic cancer.

2. OVERVIEW OF SPONSOR'S STUDY RESULTS AND REVIEWER'S ANALYSES OF SECONDARY ENDPOINTS BASED ON THE FDA MO'S ASSESSMENT

◆ In trial E012, twelve out of thirty-four patients were not qualified for the study (see sponsor Table 1 of Vol. 2.55). Using the FDA MO's assessment, 33 patients were included in the analyses. The tumor response rate was 6.1%(2/33) with 95% CI (0-14.4%). The median TTP was 51.5 days (95% CI: 49 to 107 days; range: 0-200 days) and the censoring rate was 25%(7/28). The median TTF was 57 days (95% CI: 50-58 days; range 0-212 days) and the censoring rate was 0%(0/33). These results were obtained using the FDA MO's assessment.

Following is a summary of the above three phase II single agent trials on the secondary efficacy endpoints based on FDA MO's assessment.

Table 14 - Secondary Efficacy Endpoints*

	JHAZ	JHAL	E012
OTR	4.8% (n=63)	4.5% (n=44)	6.1% (n=33)
95% C.I.	0% - 10%	0% - 11%	0% - 14%
TTP Median	61 days	85 days	52 days
95% C.I.	56 - 85 days	56 - 105 days	49 - 107 days
Censoring	13% (n=54)	10.8% (n=37)	25% (n=28)
TTF Median	57 days	57 days	57 days
95% C.I.	36-64 days	29 - 85 days	50 - 58 days
Censoring	1.6% (n=63)	0% (n=43)	0% (n=33)
SURV Median	119 days	103 days	-
95% C.I.	96 - 149 days	49 - 128 days	-
Censoring	7.9% (n=63)	14% (n=43)	-

* Evaluable patients per FDA MO.

SUMMARY AND CONCLUSIONS

THE PIVOTAL COMPARATIVE PHASE III TRIAL - JHAY.

- After the assessment on the impact of dropouts, this reviewer pointed out that the sponsor's result of a statistically significantly higher CBR response rate in the Gemzar arm over 5-FU arm (23.8% vs 4.8%) still hold. All analyses assumed that the ranking of reasons for treatment discontinuation is adequate. In addition, Dr. M. Takeuchi pointed out that 'missing data seemed to follow a nonignorable missing mechanism. The attrition rates in both treatment groups were extremely high, and the sample sizes in both arms were small. Therefore all analyses of clinical benefit response and its components have the potential to be biased. Results, therefore, should be interpreted cautiously'. He concluded that 'by the robust results obtained from the longitudinal analyses, it is concluded that the beneficial aspects in each of the three components of the clinical benefit response endpoint point toward a positive effect for Gemcitabine'.
- The FDA MO's assessment on objective tumor response (3.2% in

both Gemzar and 5-FU arms) differed from that of the sponsor's (0% in the 5-FU arm and 4.8% in the Gemzar arm). Despite this difference, i.e., with minor dates or censoring differences, the findings of a statistically significantly longer time to disease progression (p=.005, 1.19 months longer with Gemzar), time to treatment failure (p=.0018, .96 months longer with Gemzar), and survival (p=.0008, 1.46 months longer with Gemzar) in this reviewer's univariate analyses using the FDA MO's assessment were consistent with the sponsor's findings.

- From this reviewer's exploratory survival analysis, the survival advantage in the Gemzar group (mortality risk ratio) was homogeneous when patients were stratified by either pain intensity, or analgesic consumption. Homogeneity did not hold when patients were stratified by Karnofsky performance status (KPS), sponsor assessed baseline stage, or the FDA MO assessed clinical stage. Results with heterogeneous strata indicated that the survival advantage in the Gemzar arm was confined to patients with KPS greater than 70, with baseline stage 4, and without baseline liver metastasis (see **Tables 7-12**).

In summary, dropout rates in both arms were high and showed different patterns. This reviewer's analyses indicated that the higher CBR rate (23.8% for Gemzar vs 4.8% for 5-FU) observed for the Gemzar arm translated into a smaller percent of treatment discontinuations due to lack of efficacy (clinical progression or objective disease progression). This is also supported by Dr. Takeuchi's longitudinal analyses of each components of the CBR (see Attachment). In addition, based on the FDA MO's assessment of all the dates for time to event calculation, the analyses performed by this reviewer indicated that Gemzar had a longer median time to disease progression (by 1.19 months, p=.005), longer median time to treatment failure (by 0.96 months, p=.002), and longer median survival (by 1.46 months, p=.008). The survival benefit of Gemzar seemed to be mostly in the patients without baseline liver metastasis (8.4 weeks longer - without and 1.0 weeks longer - with baseline liver metastasis, p=.0001). The results of this reviewer's analyses indicated that the effect of Gemzar is statistically significant on the primary endpoint and supported by the findings on the secondary endpoints.

Sue-Jane Wang
Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco *C. Gnecco* 3/5/96

Dr. Chi *Chi*
3/5/96

cc:

NDA 20-509

HFD-150

HFD-701 Dr. Anello

HFD-150 Dr. Justice

HFD-150 Dr. Schechter

HFD-150 Ms. McCollum

HFD-344 Dr. Lisook

HFD-710 Dr. Chi

HFD-710 Mr. Orticke

HFD-710 Dr. Gnecco

HFD-710 Dr. Wang

HFD-710 Chron

SWANG/first draft:8-9-95, last draft:3/1/96/WP60-GEMZAR.NDA

This review consists of 30 pages of text, 14 Reviewer **Tables**, 5 Reviewer **Analyses**, 1 Reviewer **Figures**, 1 **Attachment**, and 4 **Appendices**, 10 tables from the sponsor.

Statistical Review and Evaluation

DATE: FEB 9 1996

NDA#: 20-509

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Gemzar (gemcitabine HCL)

DOCUMENTS REVIEWED: Undated Deskcopy of Sponsor's Section 5. Stability Studies and Unofficial Deskcopy of 12/15/95.

I. Background

The original request from Dr. Dietze (HFD-150) is dated 06/02/95. Some miscommunication delayed the proper material till 11/21/95. At that time it became apparent that the sponsor had plotted assay results without any statistical analysis. In discussion with the sponsor it was decided that the most expedited way to procede was for the sponsor to send this reviewer an unofficial copy of statistical analyses and the data for potency and related substances obtained from both the 'dry' product and the product stored reconstituted for _____

II. Sponsor's Results

As mentioned above the sponsor's plots of the assay results are insufficient for determining an expiration dating period. In the unofficial deskcopy of 12/15/95 the sponsor provided the output from various SAS PROC GLM models applied to the potency and Total Related Substance data (from both the 'dry' and reconstituted states). For the potency data of the dry substance of all _____ of 200 or 1000 mg strength and manufactured at Fegersheim, France, or at Indianapolis, US, the sponsor fitted several models concluding a parallel slopes model for all the _____ Using the batch with the highest intercept and the common (positive) slope the sponsor estimated the following amounts of percent change at _____ (Sponsor's Table 3. Summary of the Pooled Slopes):

III. Reviewer's Results

The sponsor tested for poolability of vial sizes and for manufacturing sites at $p=0.05$, not at the $p=0.25$ which is used to test for poolability of intercept or of slope. Which level of p is appropriate in this situation can be argued and this reviewer did not test for poolability of vial sizes nor of manufacturing sites but analyzed each set of batches separately. The estimated expiration dating period for each data set is listed in the attached Summary Table. At the request of the reviewing chemist, this reviewer also analyzed the related substances _____ and _____. Where the estimated expiration dating period is noted as 'o.k.' it means that the data showed no or hardly any variability within each batch, sometimes even between batches. However, in all cases, the observed values were well below the upper specification limits of _____ for Total Related Substances, of _____ for _____ and of _____ of _____. Potency specification limits were _____ label claim. Expiration dates related to the 'Dry Product' are in months. The product was also reconstituted and stored for _____. Therefore, any expiration dating periods for the reconstituted product are in hours. The storing of the reconstituted product was done in Fegersheim when the batches of the dry product were 12 months old; therefore, for these batches 'AGE' is listed as 12 months. The product was stored in reconstituted fashion in Indianapolis when the batches were new (AGE = 0), 12 and 24 months old. Therefore, there is a set of findings for each of these three ages.

Potency:

The data of the 200 mg product manufactured in Fegersheim regressed to a common slopes model. The initial fill of batch FF4H13 was somewhat higher than the other batches and based on its data the product can be expected to remain below _____ label claim for only 23 months. This is the only batch with less than 24 months of estimated expiration dating period based on 'dry potency'.

Potency stored reconstituted for _____

As mentioned above the product was also reconstituted and stored for _____. Regression lines were fitted through these data to estimate for how many hours the groups of batches can be expected to remain within its limits once reconstituted. Two 12-month-old

batches, FF4H13 of the 200 mg product from Fegersheim and D20351 of the 200 mg product from Indianapolis, can be expected to remain within specification less than the studied time span, namely _____ respectively. It needs to be determined whether these estimates and those of the remaining data sets satisfy the sponsor's claim for the storage of the reconstituted product.

Total Related Substances:

Total Related Substances can be expected to remain below the _____ limit for at least _____ with one exception. Batch FF4S93 estimated only _____. It need to be taken into consideration that the _____ batches from the 200 mg product from Fegersheim regressed here to individual lines and that batch FF4S93 had only six months of actual data. The resulting estimates for the regression line are very poor and the confidence bands extremely wide. The three observed values are well below the upper limit and more data needs to be collected before a proper expiration dating period can estimated by this batch.

For the _____ data from the 'dry product' no statistical analyses were performed by this reviewer as the data were mostly identical within a batch and often even across batches. The observed data were far below the upper limit of _____ and there seems to be no indication for them to vary much. This situation is marked as 'o.k.' in the attached Table. The lack of observed variability may be due to the limitations of the assay rather than due to no actual variation within the data. Nonetheless, their low levels do not seem to merit any concern from a statistical point of view.

Similarly, the _____ data from Fegersheim exhibited barely any variation to permit statistical analyses. The observed values also were well below the _____ upper limit and there seems to be no cause for concern from the statistical point of view. The _____ data obtained at Indianapolis exhibited greater variability such that regression analyses were meaningful to perform. The _____ part of the related substances can be expected to remain below the set limit for over _____ if the observed pattern of degradation does not change in the future.

Total Related Substances, _____ obtained when product was stored for _____

As mentioned above, Total Related Substances, _____ and _____ were also measured over _____ from the product stored in reconstituted form. As the attached Summary Table shows all batches estimated to remain below the respective specification limits well beyond the observed hours.

IV Summary and Conclusion

This product was manufactured in two strengths and at two sites. In order to avoid a potential discussion of if and at what level of significance these two factors may be pooled, this reviewer analyzed each data set separately.

Only one batch estimated an expiration dating period below the requested _____ for potency (batch _____: _____). The apparent reason for this failure is a higher initial fill.

The product was also stored in reconstituted fashion for _____. This was done at various ages of the batches, initially, when they were _____. The lowest estimated expiration date of all these data sets is _____ i.e. when reconstituted and stored, the product can be expected to remain within its percent label claim limits for at least _____.

Related substances are an issue with this product. The measures of Total Related Substances in general can be expected to remain below their upper specification limit of _____ for at least _____. There is one exception, however, where a single batch estimated only _____ expiry period. This batch had only three data points and its regression line and confidence limits are very poorly estimated. More data need to be obtained for this batch before estimating a reliable expiration dating period. The _____ data exhibited barely any variability making regression analyses nonsensical. The observed values are well below the upper limit and from a statistical point of view very little change is expected from these data. The same phenomenon was observed for the _____ data collected in France. The _____ data collected in Indianapolis were suitable for statistical analyses. Both strengths estimated extrapolated expiration dating periods of _____.

When the reconstituted product was held for _____ the related

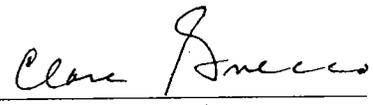
substances were also measured during these periods. _____
and _____ data from any of the batch groups exhibited very
little variation within and often between batches. Therefore, no
regression analyses were performed, but all data are well below
their respective upper limits and statistically no major change is
expected. Total Related Substances were measured finely enough for
statistical analyses. Each data set is expected to remain below the
upper specification limit for well beyond the observed _____

The above findings are summaries in the attached Table.



Roswitha E. Kelly

Concur:



Clare Gnecco, Ph.D.
Acting Team Leader



George Chi, Ph.D.
Acting Director
Division of Biometrics I

cc: Archival NDA 20-509 Gemzar (gemcitabine HCL) 200 and 1000 mg,

Lilly Research Laboratories

HFD-701/Dr. Anello

HFD-150/Division File

HFD-150/Dr. Tolgyesi

HFD-150/Dr. Dietze

HFD-150/Ms. McCollin

HFD-344/Dr. Lisook

HFD-710/Chron

HFD-710/Dr. G. Chi

HFD-710/Dr. C. Gnecco

HFD-710/Mr. Orticke

HFD-710/R. Kelly

HFD-710/RKELLY/01/26/96/wp-gemzar.rev

7.1

FEB 14 1996

Statistical Review and Evaluation
ADDENDUM

DATE: 2/14/96

NDA#: 20-509

APPLICANT: Lilly Research Laboratories

NAME OF DRUG: Gemzar (gemcitabine HCL)

DOCUMENTS REVIEWED: Volumes 1 and 3 of Sponsor's 01/09/96 Amendment to NDA Item 3.

I. Background

The reviewing chemist, Dr. Dietze (HFD-150), requested the Division of Biometrics I to review the sponsor's response to deficiency # 35 and the information submitted in Appendix XII.

II. Sponsor's Results

Deficiency # 35 deals with the request for updated stability data. The sponsor refers to the appendices for the updated raw data. His stability analysis summary shows estimated pooled slopes and predicted change in the potency and Total Related Substances at 24 months or 24 hours for the reconstituted product.

Reviewer's Results

This submission appears to be exactly what was sent to this reviewer as unofficial deskcopies on 12/15/95. Therefore, no additional comments are necessary to this reviewer's Statistical Review and Evaluation dated February 9, 1996.

IV Summary and Conclusion

In this Amendment the sponsor submitted apparently the raw data and summary results of analyses which he had submitted as an unofficial deskcopy to this reviewer in more detail in December of '95. There

are no changes to be made in this reviewer's comments and findings of her 02/09/96 Statistical Review and Evaluation which were based on the unofficial submissions.

Roswitha Kelly
 Roswitha E. Kelly

Concur:

Clare Gnecco 2/14/96
 Clare Gnecco, Ph.D.
 Acting Team Leader

George Chi 2/14/96
 George Chi, Ph.D.
 Acting Director
 Division of Biometrics I

cc: Archival NDA 20-509 Gemzar (gemcitabine HCL) 200 and 1000 mg,
 Lilly Research Laboratories

HFD-701/Dr. Anello

HFD-150/Division File

HFD-150/Dr. Tolgyesi

HFD-150/Dr. Dietze

HFD-150/Ms. McCollin^{am}

HFD-344/Dr. Lisook

HFD-710/Chron

HFD-710/Dr. G. Chi

HFD-710/Dr. C. Gnecco

HFD-710/Mr. Orticke

HFD-710/R. Kelly

HFD-710/RKELLY/02/12/96/wp-gemzar2.rev

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

MICROBIOLOGY REVIEW

CONSULTATIVE REVIEW TO HFD-150
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

JUL 21 1995

Microbiologist's Review #1
19 July 1995

A. 1. NDA 20-509

SPONSOR Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, Indiana 46285

2. PRODUCT NAMES: GEMZAR® (gemcitabine hydrochloride)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: A sterile _____ product of 200 mg strength in a 10 mL vial and 1 gram strength in a 50 mL vial. The product is to be reconstituted with sodium chloride injection without preservatives and administered by intravenous injection. Reconstituted solution must be used within 24 hours and must not be refrigerated.

4. METHOD(S) OF STERILIZATION: _____

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 1P

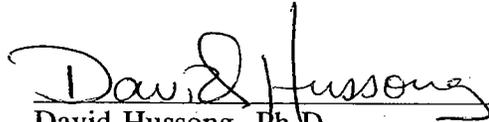
B. 1. DATE OF INITIAL SUBMISSION: 1 February 1995

2. DATE OF AMENDMENT: 17 April 1995 (subject of this review)

3. RELATED DOCUMENTS: (none cited)

C. REMARKS: The applicant has provided in this amendment a summary of CMC sections relating to manufacturing, a package insert (draft) and LAL information derived from the original submission. Additionally the applicant has provided new information to demonstrate validation of the sterility test and _____ used to manufacture the product. These were requested of the applicant in a FAX communication from HFD-150 on 7 April 1995. The FAX communication indicated that the "Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (Federal Register 58(231): 63996-64001, 3 December 1993) was also sent to the applicant, probably in a separate mailing. The applicant has not addressed "Guidelines" issues in the subject amendment.

D. CONCLUSIONS: The application is not recommended for approval for reasons of sterility assurance. Specific comments are provided in section "E. Review Notes" and in the "Microbiologist's Draft of Letter to the Applicant".


David Hussong, Ph.D. 7-21-95
PAC 7/21/95

cc:

- Original NDA 20-509
- HFD-150/Division File
- HFD-160/Consult File
- HFD-151/CSO/L. McCollum
- HFD-150/C. Schumaker
- HFD-150/Chemist/E. Tolgyesi
- HFD-150/P. Dietz
- HFD-160/D. Hussong

drafted by: D. Hussong, 07/19/95
R/D initialed by: P. Cooney, 07/21/95

E. REVIEW NOTES:

1. General Drug and Processing Descriptions. The drug product composition was described (page 40) and is shown in Table 1, below.

Table 1. *Composition of the drug solution.*

Component	Amount per 200 mg vial	Amount per 1 gram vial
Gemcitabine Hydrochloride	230 mg ^a	1.144 ^b gram
Mannitol	200 mg	1 gram
Sodium Acetate, anhydrous	12.5 mg	62.5 mg
Water for Injection, USP ^c	5 mL	25 mL

- a: *Equivalent to 202 mg of free base in activity.*
- b: *Equivalent to 1.005 grams of free base in activity.*
- c: *Water is removed during _____*

The reconstituted solution has a pH of 2.0 to 3.0.
 The draft package insert was provided on pages 3 through 30.

2. Facility and Environmental Control Descriptions. Information concerning procedures for environmental monitoring were not provided. Facility descriptions were not provided.

The product is manufactured at 2 sites:
 Lilly France S.A.
 rue de Colonel Lilly
 67640 Fegersheim, France

 Eli Lilly Technology Center
 1200 - 1555 Kentucky Avenue
 Indianapolis, Indiana

NOT SATISFACTORY

Comments. The applicant needs to describe the facilities used for _____, and _____ of the product. Filling room numbers and their locations relative to critical processes need to be identified, and product and component flow should be summarized in this context. A floor plan would be helpful. Environmental quality specifications for the _____ areas should be provided. Specifications relating to the microbiological quality of these environments should be summarized. Environmental control specifications should also address the water used in compounding drug product, including its preparation, storage (time, temperature, etc.) and microbiological limits.

3. Manufacturing and Product Flow. Descriptions of equipment used in the _____ relative to the general flow of product components were not provided for

either of the facilities. The drug product is compounded in water for injection and the pH is adjusted. The containers are filled and _____ Filtered nitrogen is used to break the vacuum. Stoppers are treated with silicone oil to facilitate seating.

NOT SATISFACTORY

Comments. Descriptions of the process at each facility should include the equipment used for critical operations (ovens, tunnels, autoclaves, filling machines, stopper placement mechanisms, lyophilizers and cappers). Process control specifications should be described to indicate storage periods and conditions for non-sterile product solutions, and storage limits and conditions for _____ Sampling for solution bioburden and specifications for bioburden should be provided. If the product solution is filtered as a sterilization method, the filtration method (including specifications for the product filter, filter flow rate or pressure, and time of filter use) should be summarized. An overall process time limit for solutions (from compounding to the start _____ should be specified.

4. Environmental Monitoring. Data and methods were not provided in the submission or as part of the media fill summary.

NOT SATISFACTORY

Comments. Microbiological methods for collecting samples and cultivating organisms from air, surfaces, personnel, bulk product solution and water should be provided. The frequency of such testing should be summarized.

5. Components and In-process Sterilization. Specifications for component sterilization were not found in the submission.
 - a. Container/Closure System. The both product strengths use a _____ container and a _____ Product labelling (page 30) states the 200 mg strength is in a 10 mL vial and the 1 gram strength is in a 50 mL vial. However, section 2.4 (container-closure system, page 44) states the vials are 5 mL and 25 mL, respectively. Sterilization methods and their validation were not found.
 - b. Filling Equipment. No description or validation of sterilization processes was provided.
 - c. Filter Units. No descriptions of the sterilization methods or validation were found.

NOT SATISFACTORY

Comments. Information describing methods for sterilization and their validations should be described. Summaries of sterilization validation data should be provided for each major process.

These should address sterilization of containers, closures, product solution, filters and processing equipment.

6. Process Validation Studies.

- a. Solution Storage. No description or validation was provided.
- b. Media Fills. Page 46 summarized media fills with data in tabular form. A note indicates that neither facility used the Gemcitabine container and closure system, but instead used a system described as a worst case.

Media fills _____ manufactured in Indianapolis were reported having been performed on fill line 6 and Freeze Dryer line 5. The vials were _____ and _____ using closure _____. These fills were performed from July through November 1994 and each fill consisted of over _____. There were no reported positives. The applicant states growth promotion tests were acceptable. One routine media fill : _____ for fill line 6 was described.

- c. Product Filtration. No description was provided.
- d. Closure Integrity. No studies were described.

NOT SATISFACTORY

Comments. Solution storage limits should be indicated and storage beyond 24 hours should be validated.

Product solution filtration should be validated. The filter and its operating parameters (pressure, flow, time limits, and integrity tests) are to be specified in the manufacturing instructions, and these process specifications should be validated.

The integrity of the barrier to microbial ingress afforded by the container and closure system should be demonstrated.

Media fill data were not clearly related to the product filling process. The containers used and the process should be compared to indicated why these were a "worst case". Although the media were described as tested for growth promotion, this is not a positive control which is necessary for any experiment.

- 7. Antimicrobial Preservatives-Effectiveness Test. Not applicable.
- 8. Product Release Specifications. Test sites for the cartridge are Lilly France in Fegersheim, and for the vial presentation Eli Lilly and Company (Lilly Technology Center, Indianapolis, and Lilly Corporate Center, Indianapolis).

4 _ Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA

MAR 26 1996

25 March 1996

A. 1. NDA 20-509

SPONSOR Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

2. PRODUCT NAMES: GEMZAR® (gemcitabine hydrochloride)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile, _____
product of 200 mg strength in a 10 mL vial, and 1 gram strength in a 50 mL vial.
The product is to be reconstituted with sodium chloride injection without
preservatives and administered by intravenous injection. Reconstituted solution
must be used within 24 hours and must not be refrigerated.

4. METHOD(S) OF STERILIZATION: _____

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 1P

B. 1. DATE OF INITIAL SUBMISSION: 1 February 1995

2. DATE OF AMENDMENTS:

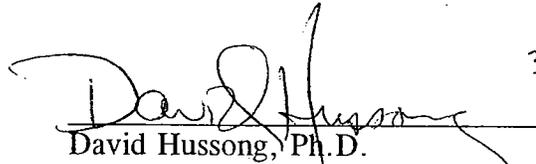
17 April 1995 (subject of Microbiologist's Review #1),
26 July 1995 (subject of this review), and
9 January 1996 (also subject of this review).

3. RELATED DOCUMENTS: Microbiologist's Review #1 dated 19 July 1995

4. ASSIGNED FOR REVIEW: 2 February 1996

C. REMARKS: The applicant has provided the 26 July 1995 amendment in response to a FAX communication on 7 April 1995 from the CSO. The FAX conveyed microbiology concerns relevant to filing the application. The applicant did not respond to that FAX until after Microbiologist's Review #1 was completed, and Microbiologist's Review #1 resulted in many deficiencies. The applicant's amendment dated 9 January 1996 replies to the agency's letter conveying deficiencies from Microbiologist's Review #1, although most replies refer to the 26 July 1995 amendment.

D. CONCLUSIONS: The application is not recommended for approval for reasons of sterility assurance. Specific comments are provided in section "E. Review Notes" and in the "Microbiologist's Draft of Letter to the Applicant".


David Hussong, Ph.D. 3-25-96
PAC 3/26/96

cc:

HFD 805/Consult File
HFD 150/Original NDA
HFD 150/CSO/L. McCollum
HFD 150/Rev. Chemist/P. Dietz
HFD 150/Chem TL/E. Tolgyesi
HFD 805/D. Hussong

Drafted by: D. Hussong, 03/25/96
R/D initialed by: P. Cooney, 03/26/96

Filename, c:\nda\20-509.rv2

17 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

PHARMACOKINETIC REVIEW

PHARMACOKINETIC SECTION

NDA 20-509

Gemcitabine Injection 200mg/10mL, 1g/50mL

Eli Lilly

Submission Date: February 1, 1995

Reviewer: Lydia C. Kaus, M.S., Ph.D.

Type of Submission: 1P

Proposed Dose: 1000 mg/m² IV for 30 minutes weekly

Synopsis:

The disposition of gemcitabine was studied in seven studies (JHAZ, JHAY, JHAA(ext), JHAP, JHAR, JHAQ and EO18), two of which were Phase I studies (JHAA and JHAP) using various IV infusion schedules over a wide range of doses and up to 62 weeks of therapy. A total of 353 patients were assessed pharmacokinetically, ranging in age from 29 to 79 years of age and composed of 121 women and 232 men. A metabolism and excretion study was conducted in 5 patients in JHAP using radiolabelled gemcitabine. Gemcitabine is metabolized intracellularly by deoxycytidine kinase and other nucleoside kinases to the active forms, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). An inactive uridine derivative, 2'-deoxy-2',2'-difluorouridine or dFdU, is also produced through metabolism by cytidine deaminase. Radioactivity recovered within 1 week in 5 patients ranged from 92 to 98% of the administered dose. The mean red blood cell to plasma concentrations of ¹⁴C-gemcitabine ranged from 0.60 to 0.83. Urinary excretion accounted for >99% of the recovered dose and < 1% of total radioactivity in the feces. Potential drug interactions were not studied.

Population pharmacokinetic analysis using NONMEM allowed the inter-patient variability in gemcitabine clearance and distribution to be defined. The influence of covariates such as age, creatinine clearance and gender on the pharmacokinetics of gemcitabine were addressed. Some attempt was made to study the pharmacokinetic-toxicokinetic-pharmacodynamic relationships that may exist. The

were used throughout the clinical trials. The _____ is the same

_____ From the population analyses of the seven studies (JHAZ, JHAY, JHAA(ext), JHAP, JHAR, JHAQ and EO18), where 35% of the database was composed of pancreatic patients, gemcitabine plasma clearance at baseline (without consideration of age nor gender) was 122 L/hr/m² (± SE 26) with an interindividual variability of 52%. Volume of distribution of central compartment for males was found to be 17.5 L/m² ± SE 1.55 with an interindividual variability of 92%. Females were found to have a volume of distribution 70 % that of males. The volume of distribution of the peripheral compartment was 370 L/m² after long infusions (infusion time greater than 1.2 hours) and this was 47 L/m² after short infusions (infusion time less than 1.2 hours). The difference in volume of distribution after

different infusion times may be due to differences in equilibration in the tissues. The distributional blood flow (Q) was found to be 225 L/hr (\pm SE 26) with an interindividual variability of 18%. The residual variability was 41%. All variabilities were modeled using a proportional error model.

Population analyses of the pancreatic cancer patient population (studies JHAY and JHAZ) which included data on the metabolite gave inflated interindividual variance estimates with the five compartment model used in the Phase I studies, therefore a four compartment model was selected. The four compartment model consisted of two compartments each for gemcitabine and the metabolite dFdU. The metabolite population pharmacokinetic results were questionable since there tended to be overinflation of some of the pharmacokinetic parameters being estimated and unrealistic estimations in physiological terms of some of the others. The metabolite kinetics were best described by the Phase I traditional 2-stage analysis. Three compartments were used to represent the metabolite (one central and two peripheral), resulting in 18.1 L/m² for the central compartment's volume of distribution and 88.9 L/m² and 43.4 L/m² for the peripheral compartments' distributions. The apparent terminal half-life was estimated to be 65.3 hr and clearance was 2.5 L/hr/m².

In the population analyses across the seven studies, gemcitabine clearance was shown to be influenced by age and gender:

Age (yr)	Men (L/h/m ²)	Women (L/h/m ²)
29	92	69.4
45	75.7	57
65	55.1	41.5
79	40.7	30.7

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. Renally impaired patients were not studied per se; gemcitabine is rapidly metabolized to dFdU and less than 10 % is excreted unchanged in the urine. Therefore impaired renal function would not be expected to affect gemcitabine excretion to any great extent. The metabolite, dFdU does not undergo additional biotransformation and is eliminated in the urine. No hepatically impaired patients were studied per se, however correlations with clinical factors such as ALT and AST were explored. Cytidine deaminase, the enzyme that is responsible for the metabolism of gemcitabine to dFdU, is found in several tissues including blood. The effect of liver dysfunction on the elimination of gemcitabine must be considered in the context of the distribution of cytidine deaminase in several tissues. The assay measuring gemcitabine and the inactive metabolite, dFdU was acceptable. Possible relationships between toxicity and the disposition of dFdU were explored. Peak dFdU concentrations and up to 29 clinical parameters were compared. The WBC WHO grade toxicity was significantly negatively correlated with dFdU concentrations. This

association was thought to be due to a reflection of exposure to the parent rather than toxicity of the metabolite, since dFdU is not active.

Recommendation:

The Division of Biopharmaceutics has reviewed the Pharmacokinetic section of the NDA submission and has found that the information contained is adequate for approval.

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BACKGROUND:

Gemcitabine (2'-deoxy-2',2'-difluorocytidine or LY188011) is proposed for use as first line treatment of advanced or metastatic adenocarcinoma of the pancreas in chemo-naïve patients, or second line treatment of advanced pancreatic cancer in 5-FU refractory patients. Clinical trials JHAY and JHAZ were in pancreatic patients; these were also studied using sparse sampling and population pharmacokinetic analysis. Gemcitabine is a fluorine-substituted cytarabine (Ara-C) analog. It is therefore a prodrug, which is phosphorylated intracellularly by deoxycytidine to active gemcitabine diphosphate and triphosphate.

SUMMARY OF

BIOAVAILABILITY/PHARMACOKINETIC/PHARMACODYNAMICS:

I. BIOAVAILABILITY/BIOEQUIVALENCE:

This is an IV formulation. The _____ was used throughout the clinical trials or formulations that were _____. The _____ is the _____.

II. PHARMACOKINETICS:

[¹⁴C]-gemcitabine was administered to five patients and radioactivity was measured by means of liquid scintillation spectrometry in plasma, urine, feces and breath samples. Breath samples collected for 5 hours in the first two patients showed negligible amounts of radioactivity and so no further breath samples were collected for the other patients. Radioactivity recovered within 1 week in 5 patients ranged from 92 to 98% of the administered dose. The mean red blood cell to plasma concentrations of ¹⁴C-gemcitabine ranged from 0.60 to 0.83. Urinary excretion accounted for >99% of the recovered dose and < 1% of total radioactivity in the feces. Radioactivity measured was the total for gemcitabine and 2-dFdU. The half-lives for radioactivity in plasma and blood were 68.3 and 65.3 hours respectively. The mean C_{max} for gemcitabine was 18.2 μg/mL occurring 1 minute after the completion of infusion. The C_{max} for dFdU ranged from 27.6 to 51.7 μg/mL, occurring 3 to 15 minutes post-infusion (Clinical Study B9E-MC-JHAP).

Data were fitted to a two compartment model with first order elimination. When the metabolite (dFdU) data were taken into account a five compartment model was found to be appropriate in the single dose Phase I studies. Several datasets were analyzed using NONMEM. From the population analyses of the seven studies (JHAZ, JHAY, JHAA(ext), JHAP, JHAR, JHAQ and EO18), where 35% of the database was composed of pancreatic patients, gemcitabine plasma clearance at baseline (without consideration of age nor gender) was 122 L/hr/m² (± SE 26) with an interindividual variability of 52%. Volume of distribution of central compartment for males was found to be 17.5 L/m² ± SE 1.55 with an interindividual variability of 92%. A factor accounting for gender resulted in females having a volume of distribution 70 % that of males. The volume of distribution of the peripheral compartment was 370 L/m² after long infusions (infusion time greater than 1.2 hours) and a factor accounting for infusion duration showed that this was 47 L/m² after short infusions (infusion time less than 1.2 hours). The distributional blood flow (Q) was found to be 225 L/hr (± SE 26) with an interindividual variability of 18%.

The residual variability was 41%. All variabilities were modeled using a proportional error model.

Population analyses of the pancreatic cancer patient population (studies JHAY and JHAZ) which included data on the metabolite gave inflated interindividual variance estimates with the five compartment model used in the Phase I studies, therefore a four compartment model was selected. The four compartment model consisted of two compartments each for gemcitabine and the metabolite dFdU. The metabolite population pharmacokinetic results were questionable since there tended to be overinflation of some of the pharmacokinetic parameters being estimated and unrealistic estimations in physiological terms of some of the others. The metabolite kinetics were best described by the Phase I traditional 2-stage analysis. Three compartments were used to represent the metabolite (one central and two peripheral), resulting in 18.1 L/m² for the central compartment's volume of distribution and 88.9 L/m² and 43.4 L/m² for the peripheral compartments' distributions. The apparent terminal half-life was estimated to be 65.3 hr and clearance was 2.5 L/hr/m².

In the population analyses across the seven studies, gemcitabine clearance was shown to be influenced by age and gender:

Age (yr)	Men (L/h/m ²)	Women (L/h/m ²)
29	92	69.4
45	75.7	57
65	55.1	41.5
79	40.7	30.7

III. METABOLISM:

Gemcitabine is metabolized intracellularly by deoxycytidine kinase and other nucleoside kinases to the active forms, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). An inactive uridine derivative, 2'-deoxy-2',2'-difluorouridine or dFdU, is also produced through metabolism by cytidine deaminase.

IV. DOSE/DOSAGE FORM PROPORTIONALITY:

In the traditional study JHAA (ext.) and in the population analyses of studies JHAQ and JHAR doses ranged from 1000 to 2500 mg/m² and 500 to 3600 mg/m² with infusion times ranging from less than 70 minutes and 70 to 285 minutes respectively. Clearance was independent of the infusion rate.

V. SPECIAL POPULATIONS:

a. Renal Impairment:

Renally impaired patients were not studied per se; gemcitabine is rapidly metabolized to dFdU and less than 10 % is excreted unchanged in the urine. Therefore impaired renal function would not be expected to affect gemcitabine excretion to any great extent. The metabolite, dFdU does not undergo additional biotransformation and is eliminated in the urine. Peak dFdU concentrations were compared with 29 clinical variables including creatinine clearance. No clear relationship was found with creatinine clearance and peak dFdU concentrations. Creatinine clearance as a covariate was also tested in the population analyses of JHAY and JHAZ, the trials that had pancreatic cancer patients. Difficulties in the model definition for the pancreatic study population, such as expansive typical values for parameters and inability to obtain reasonable confidence intervals, precluded the inclusion of covariates.

b. Hepatic Impairment:

No hepatically impaired patients were studied per se, however correlations with clinical factors such as ALT and AST were explored. Cytidine deaminase, the enzyme that is responsible for the metabolism of gemcitabine to dFdU, is found in several tissues including blood. The effect of liver dysfunction on the elimination of gemcitabine must be considered in the context of the distribution of cytidine deaminase in several tissues.

c. Elderly and gender:

In the population analyses across the seven studies, gemcitabine clearance was shown to be influenced by age (and gender):

Age (yr)	Men (L/h/m ²)	Women (L/h/m ²)
29	92	69.4
45	75.7	57
65	55.1	41.5
79	40.7	30.7

d. Race:

More than 90% of the patients were Caucasian, therefore interpretation of results for differences in pharmacokinetics must be taken in the light of the small number for comparison. Clearance and volume of distribution for the central compartment fall within the range for the total population of all seven studies. Therefore ethnic differences in pharmacokinetics are not apparent. Ethnicity was not a strong predictor in the stepwise regression analyses in covariate analysis to explain variability in cytidine deaminase.

VI. DRUG INTERACTIONS:

No drug interactions were studied.

VII. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

Possible relationships between toxicity and the disposition of dFdU were explored. Peak dFdU concentrations and up to 29 clinical parameters were compared. The WBC WHO grade toxicity was significantly correlated with dFdU concentrations. Stepwise linear regression analysis and logistic analysis were the statistical methods used. This association was thought to be due to a reflection of exposure to the drug rather than toxicity of the metabolite, since dFdU is not active. All analyses undertaken were of an exploratory nature and further investigations by the sponsor using these preliminary results are ongoing.

VIII. FORMULATIONS:

Gemcitabine will be manufactured as a lyophilized powder, consisting of _____ base drug, mannitol _____ anhydrous sodium acetate _____ Both a 200 mg and a 1G vial will be available and these are _____ clinical and pharmacokinetic studies.

IX. DISSOLUTION:

N/A

X. ASSAY:

_____ Weighted least squares (1/x) was used to fit a calibration curve. Linearity, accuracy and precision were acceptable. The internal standard showed some interference, however since peak height and not peak areas were used in the calibration curves and the interfering peak was substantially less in peak height than the internal standard, the assay was acceptable.

**Appears This Way
On Original**

General Comments:

1. The sponsor needs to comment on the potential toxicity or otherwise of the metabolite dFdU in renally or hepatically impaired individuals. The much longer half-life of the metabolite under these circumstances may lead to substantially higher and possibly toxic levels.
2. The sponsor should undertake some type of analysis to relate cumulative dose with the toxicity/toxicity parameters recorded for the drug.
3. In general the lack of information on pharmacokinetic toxicodynamic relationships makes it difficult to assess dosing and dosing recommendations.
4. There is a lack of information on potential drug interactions. The sponsor should study potential drug interactions with agents likely to be concomitantly used in the patient population such as etoposide and cisplatin.
5. The sponsor should keep the following in mind for future submissions where population analyses are used: provide the control files for the final models and runs for each of the databases analyzed, flat ASCII files on the datasets used in these and summary tables alone illustrating the results from other runs not selected as the final model. A hard copy of the first page of each dataset with the individual variable column identified would also be useful. Any SAS programs and datasets used in analyses need to be provided with the submission.
6. The sponsor may want to use GAM (generalized additive modeling) or similar analyses to allow for nonlinearity and heterogeneous variances to model the relationship between individual PK parameter estimates and covariates. Then the sponsor can use the information to build a population model using NONMEM.
7. The sponsor may want to try mixture modeling with NONMEM if there is a possibility of polymorphism in the population.

Labelling Comments:

"CLINICAL PHARMACOLOGY

Human Pharmacokinetics-- Gemcitabine disposition was studied in five patients who received a single 1000 mg/m²/30 minute infusion of radiolabeled gemcitabine. Within 1 week, 92% to 98% of the dose was recovered.

Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine have been examined in 353 patients.

Pharmacokinetic parameters were derived using data:

Gemcitabine pharmacokinetics are linear."

1. The above statements are acceptable.
-
-

with pancreatic cancer.

"A 2-compartment model" _____

2. The above statements should be removed: _____

" Population pharmacokinetic analyses of combined single and multiple dose studies" _____

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Clearance was affected by gender and age. _____

3. The statement which recommends _____

Volume of distribution

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.^{27,28}

PRECAUTIONS

Patients with Renal and Hepatic Impairment--See Dosage and Administration. Gemzar should be used with caution.

DOSAGE AND ADMINISTRATION

Gemzar is for intravenous use only.

Adults--Gemzar should be administered intravenously at a dose of 1000 mg/m² for 30 minutes once weekly for up

Laboratory evaluation of renal and hepatic function, _____

4. _____

5. Some comment needs to be made under _____

6. Some mention needs to _____



8/4/95
8/15/95
10/3/95

Lydia C. Kaus, M.S., Ph.D.
Pharmacokinetics Evaluation Branch

Biopharm Day (9/6/95): Attendees: Mehta, Collins, Ludden, Fleischer.

RD Mmm 8/11/95
FT Mmm 10/5/95

Mehul Mehta, Ph.D., Section Head.

- cc NDA 20-509 file
- HFD-150: Schechter
- HFD-150: Div. File
- HFD-150: McCollum
- HFD-426: Biopharm/Drug File
- HFD-426: Biopharm/Mehta
- HFD-426: Biopharm/Fleischer
- HFD-426: Biopharm/ChenL
- HFD-340: Viswanathan

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

**PHARMACOLOGY AND TOXICOLOGY
REVIEW (S)**

JAN 23 1996

Division of Oncology and Pulmonary Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Original Review No. 1

NDA: 20-509

Date of Submission: February 2, 1995
Received by Reviewer: January 5, 1995
Date of Original Amendment: October 2, 1995

Information to be conveyed to sponsor: Yes (x), No ()

Reviewer: Doo Y. Lee Ham, Ph. D.

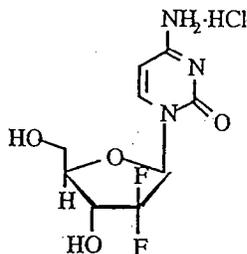
Date Review Completed: August 18, 1995

Applicant: Eli Lilly and Company
Indianapolis, IN 46285

Drug Name: Gemzar (Gemcitabine Hydrochloride; dFdC)
Code Names: LY188011; LY264368

Chemical Name: 2',2'-difluorodeoxycytidine monohydrochloride (dFdC)

Structure:



Molecular Weight: 299.66

Related IND: IND 29,653

Class: A Nucleoside analog/Antineoplastic agent

Indication: Gemzar is indicated as first-line treatment for patients with advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemzar is indicated for patients with 5-FU-refractory pancreatic cancer. The recommended dose for gemcitabine is 1000 mg/m² administered as a 30-minute infusion. The doses are given weekly for 7 weeks followed by a rest week, then weekly for 3 weeks every 4 weeks thereafter.

Clinical Formulation: Vials of Gemzar[®] contain either 200 mg or 1 g of gemcitabine hydrochloride (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 material. HCl and/or NaOH may have been added for pH adjustment.

Route of Administration: Intravenous

Previous Review, Dates and Reviewer:

Original Review	3/26/87	C. Joseph Sun
Review #2	4/13/87	C. Joseph Sun
Review #3	8/12/87	C. Joseph Sun

Studies Reviewed Previous Submissions:

- I. Pharmacology:
 - antitumor activity
 - cell kinetic studies
 - effects on urine electrolytes
 - effect in isolated cardiac muscle prep in vitro
 - cardiovascular and respiratory effects
 - CNS effects
- II. Pharmacokinetics:
- III. Toxicology:
 - single i.v. dose lethality in mice
 - single i.v. dose lethality in rats
 - 3-month i.p. toxicity in mice
 - 3-month i.v. toxicity in dogs
- IV. Genotoxicity:
 - Ames test
 - Induction of DNA repair synthesis
 - Mouse lymphoma assay
 - Sister chromatid exchange in vivo

Studies Reviewed with This Submission:

- I. Pharmacology:
 - A. Evaluation of the Antitumor Activity of Gemcitabine (2',2-Difluoro-2'-deoxycytidine), Larry W. Hertel et al. *Cancer Res.* 50:4417-4422, 1990
 - B. Comparison of Antineoplastic Activity of 2', 2'-Difluorodeoxycytidine and cytosine arabinoside against human myeloid and lymphoid leukemic cells), David Y Bouffard et al. *Anti-Cancer* 2:49-55, 1991
 - C. Modulatory Activity of 2',2'-Difluorodeoxycytidine on the Phosphorylation and Cytotoxicity of Arabinosyl Nucleosides, Varsha Gandhi and William Plunkett. *Cancer Res.* 50:3675-3680, 1990
 - D. Concentration and time dependent growth inhibition and metabolism in vitro by 2',2'-Difluorodeoxycytidine (Gemcitabine). Ruiz van Haperen et al. *Purine and Pyrimidine Metabolism in Man VII Part A.* pp 57-60.
 - E. Activity of 2',2'-Difluorodeoxycytidine (Gemcitabine) against human tumor colony forming units, Axel-R Hanauske et al. *Anti-cancer Drugs* 3:143-146, 1992
 - F. Evaluation of new anticancer agent against the MIA PaCa-2 and PANC-1 human pancreatic carcinoma xenografts, Richard M. Schultz et al. *Once. Res.* 5:223-228, 1993
 - G. Deoxycytidine protects Normal bone Marrow Progenitors against Ara-C and Gemcitabine

Cytotoxicity without Compromising Their Activity against Cisplatin-Resistant Ovarian Carcinoma Cancer Cells. Kapil Bhalla et al. *Gynecologic Oncol.* 45:32-39, 1992

- H. The Influence of the schedule and the dose of Gemcitabine on the Antitumor Efficacy in Experimental human Cancer, E. Boven et al. *Br J Cancer* 68:52-56, 1993
 - I. Preclinical in Vivo Activity of 2', 2'-Difluorodeoxycytidine (Gemcitabine) Against Human Head and Neck Cancer, BJM Braakhuis et al. *Cancer Res.* 51:211-214, 1991
 - J. Comparison of the Antitumor Activity of Gemcitabine and Ara-C in a Panel of Human Breast, Colon, Lung and Pancreatic Xenograft Models, Ronald L. Merriman et al. *Preclinical Pharmacology Report No. 35*
 - K. Evaluation of new anticancer agent against the MIA PaCa-2 and PANC-1 human pancreatic carcinoma xenografts, Richard M. Schultz et al. *Once. Res.* 5:223-228, 1993
 - L. Inhibition of Proliferation of Cells in Culture by Gemcitabine, *Preclinical Report No. 2*
 - M. Action of 2', 2'-Difluorodeoxycytidine on DNA synthesis, Peng Huang et al. *Cancer Res.* 51:6110-6117, 1991
- II. Pharmacokinetics:**
- A. Plasma pharmacokinetics of LY188011 and its Deaminated Metabolite, 198791, in B6C3F1 Mice Administered a Single Intravenous Dose of 20 mg/kg of 14C-LY188011 Hydrochloride, *ADME Study Report 7*
 - B. Plasma pharmacokinetics of LY188011 and it metabolite 198791 in Fischer 344 rats following a single intravenous administration of 10 mg/kg of 14C-LY188011 HCl, *ADME Study Report 21*
 - C. Plasma pharmacokinetics of LY188011 and its metabolite, 198791 in Beagle dogs following a single intravenous administration of 5 mg/kg of 14C-LY188011 (Study DO9986), *ADME Study Report 27*
 - D. Tissue Concentrations of Radioactivity in B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 11*
 - E. Tissue Concentrations of Radioactivity in Tumor Bearing B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 12*
 - F. Tissue Concentrations of Radioactivity in Fischer 344 Rats Following a Single Intravenous Administration of 10 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 24*
 - G. Evaluation of The In Vitro Protein Binding of 14C-LY188011 in Mouse, Rat, Dog, Monkey and Human Plasma, *ADME Study Report 18*
 - H. Urinary Metabolites of LY188011 Isolated From B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 13*
 - I. Urinary Metabolites of LY188011 Isolated From Fischer 344 Rats Following a Single Intravenous Administration of 10 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 25*
 - J. Urinary Metabolites of 14-C-LY188011 Isolated from Beagle Dogs Following a Single Intravenous Administration of 5 mg/kg of 14-C-LY188011 Hydrochloride, *ADME Study Report 29*
 - K. Elimination of Radioactivity From B6C3F1 Mice Following Intravenous Administration of 20 mg/kg of 14C-LY188011 Hydrochloride, *ADME Study Report 16*
 - L. Elimination of Radioactivity from Fischer 344 Rats Following Intravenous Administration of 10 mg/kg of 14C-LY188011 Hydrochloride, *ADME Study Report 26*
 - M. Elimination of Radioactivity from Beagle Dogs Following Intravenous Administration of

5 mg/kg of 14C-LY188011 Hydrochloride, ADME Study Report 30

III. Toxicology:

- A. The Acute Toxicity of compound 190130, an Impurity of Gemcitabine given intravenously to CD-1 mice, Study No. M05991 and M06091
- B. The Acute Toxicity of compound 282037, an Impurity of Gemcitabine given intraperitoneally to Fischer 344 rats, Study No. R27790
- C. The Acute Toxicity of compound 198791, the Major Degradation Product of Gemcitabine HCl given Intravenously to Fischer 344 rats, Study No. R19491
- D. An Acute Toxicity Study of Gemcitabine HCl given by bolus intravenous administration to dogs, Study No. D02791
- E. A Chronic Toxicity Study of Gemcitabine HCl given intraperitoneally to CD-1 mice for 6 months with a 2-month reversibility study, Study No. M25589 and M25689
- F. A Chronic Toxicity Study of Gemcitabine HCl given intraperitoneally to CD-1 mice for 6 months with a 6-week reversibility study, Study No. M06591
- G. A Chronic Toxicity Study of Gemcitabine HCl given intravenously to beagle dogs for 6 months with a 6-week reversibility study, Study No. D00191

IV. Special Toxicity Studies:

- A. Evaluation of the Immunogenicity of LY188011 HCl in male guinea pigs, Study No. G02588 and G02888
- B. In Vitro Hemolysis and Serum Flocculation tests using Gemcitabine HCl in pooled whole blood and serum beagle dogs and rhesus monkeys, Study No. D05189 and P04889
- C. Acute Dermal Irritation study of Gemcitabine in NZW rabbits, study No. B01492

V. Reproductive Toxicology:

- A. A 3-Month Male Fertility Study of Gemcitabine HCl given intraperitoneal injections to B6C3 mice, Study No. M00689
- B. A Segment I Female Fertility Study of Gemcitabine HCl given intravenous injections to CD-1 mice, Study No. M04190
- C. A developmental toxicology study of Gemcitabine HCl given intravenously to female CD-1 mice, Study No. M03090
- D. A Developmental toxicology study of Gemcitabine HCl given intravenously to NZW rabbits, Study No. B00291
- E. A perinatal/postnatal Study of Gemcitabine HCl given intravenously to CD-1 mice, Study No. M19390

VI. Mutagenicity Studies:

- A. The effect of Gemcitabine HCl on the induction of reverse mutations in Escherichia Coli using the Ames test, Study No. 910430AMS2499
- B. The effect of Gemcitabine HCl on the in Vitro Induction of Chromosome Aberrations in CHO cells, Study No. 910424CAB2499 and 910530CAB2499
- C. The effect of Gemcitabine HCl on the in Vivo Induction of Micronuclei in bone marrow of ICR mice, Study No. 910625MNT2499

*Portions of this review were excerpted directly from the sponsor's submission.

Overall Summary and Evaluation:

Gemcitabine (LY188011 HCl; dFdC) is a novel pyrimidine antimetabolite that possesses antitumor activity. Like Ara-C, gemcitabine is a deoxycytidine analog that is cell cycle specific. The mechanism of action of gemcitabine is not fully understood. In vitro cell cycle kinetic studies indicated that gemcitabine inhibits proliferation at the early S phase of cell cycle in CHO and LY5178K leukemia cells. Cellular pharmacology studies indicated that gemcitabine is converted to the triphosphate metabolite (dFdCTP) similar to the ara-CTP, metabolite of ara-C. In several cell types, the accumulation of dFdCTP was more rapid and exceeds the concentration of ara-CTP. Tumor cells were able to eliminate the ara-CTP much more rapidly than dFdCTP. Ara-C has been the drug of choice for the treatment of adult acute leukemias and other hematological malignancies but it has little or no activity against human solid tumors.

Gemcitabine has broad spectrum antitumor activity against murine leukemias (L1210, P388, P1534J, Friend), murine solid tumors (X5563 myeloma, CA-755 adenocarcinoma, M-5 ovarian carcinoma, 6C3HED lymphosarcoma, B-16 melanoma) and human tumor xenograft models (LX-1, CX-1, MX-1, PaCa-2, PANC-1) both in vitro and in vivo. Schedule dependency of antitumor activity of gemcitabine was demonstrated in NMRI nude mice. The Q3D x 4 schedule was found to be superior to weekly or daily injections with significant antitumor effect observed in SCCHN tumor lines.

The pharmacokinetics, metabolism, and disposition of gemcitabine was studied following a single intravenous administration of the drug in mice, rats, and dogs. All three species metabolize gemcitabine to the uracil metabolite by cytidine deaminase. However, deamination in the mouse and dog was more extensive than in the rat. In the mouse, gemcitabine is rapidly metabolized and excreted with a plasma half-life of @ 15 min (greater than 80% of the dose is accounted for in urine as the uridine metabolite and its glucuronide). In the rat, gemcitabine is much less rapidly metabolized with a plasma half-life of @ 8 hr and the pattern of metabolism is different with only 13% of the dose excreted in urine as the uridine metabolite and its glucuronide. The metabolic pattern in the dog is similar to that of the mouse and human with more than 90% of the dose accounted for in the urine as the uridine metabolite and its glucuronide. To compare pharmacokinetics (based on mg/m²), the corrected AUC for gemcitabine in the rat is 30.36 ug.hr/ml (highest), in the mouse 9.27 ug.hr/ml, in man 8.2 ug.hr/ml and in the dog 8.07 ug.hr/ml. In the toxicity studies the rat is most sensitive species, suggesting gemcitabine toxicity is more related to the AUC than to C_{max}. Gemcitabine has been shown to be least toxic in the dog consistent with the lower AUC value in these species.

The acute toxicity of gemcitabine HCl was studied in mice, rats, and dogs using the intravenous route of administration. No mice died at a single dose level of 500 mg/kg. Clinical signs included poor grooming, weight loss, leg weakness and hair loss. In rat, toxic effects of gemcitabine included dose-related deaths, poor grooming, hypoactivity, hair loss, diarrhea, swollen face and emaciation. Pathology findings included hemorrhages in the lung and intestinal mucosa, splenomegaly (hematopoietic hyperplasia) and thymic atrophy. A single i.v. bolus dose of 3 to 24 mg/kg gemcitabine in beagle dogs produced abnormal stools and reversible neutropenia. The MLD in acute studies include: 1) > 500 mg/kg, i.v. in mice; 2) 236 mg/kg, i.v. in rats; and 3) > 24 mg/kg i.v. in dogs. Gemcitabine was acutely more toxic in rats than in mice.

Three month subacute studies were performed in the mouse and dog. Mice were given i.p. doses of 1 mg/kg daily, 5, 20 mg/kg biweekly, and 40 mg/kg weekly doses. Dogs received i.v. doses of 0.1 mg/kg daily, 1.5 mg/kg biweekly, and 3 mg/kg weekly for 3 months. The major toxicity in both species was hematologic. Increased spleen weights were partially normalized, but testicular weight remained depressed at the end of recovery. Histologically, splenic and testicular lesions (hypoplasia, degeneration) were seen in all treatment groups. In the 3-month study a daily dose of 1 mg/kg was more toxic than biweekly, or weekly dose. Three month dog studies were conducted at 0.1 mg/kg daily, 1.5 mg/kg biweekly, or 3 mg/kg weekly dose levels. In dogs at all dose levels and schedules, no major toxicity was seen. Mild g.i. toxicity (abnormal stool) and minimal hematologic toxicity with leucopenia and neutropenia were observed with the 1.5 mg/kg biweekly doses. Pathologic lesions include hypoplasia of the thymus and testes in the 1.5 mg/kg group.

Six month chronic studies were conducted in mice using the i.p. doses of 0.5 mg/kg daily, 5 mg/kg biweekly and 40 mg/kg weekly doses. The toxicity observed in this study was similar to that observed in the previous 3-month study. A daily dose of 0.5 mg/kg (and 0.3 mg/kg) resulted in severe hematologic toxicity whereas a biweekly or weekly schedule at much larger doses were well tolerated in mice. In a six month chronic study, dogs received i.v. doses of 0.004-0.2 mg/kg daily and 3 mg/kg weekly doses. All dogs survived and tolerated daily or weekly doses for 6 months with no major toxicity.

In both the 3- and 6-months studies, a daily dose schedule resulted in severe toxicity, whereas interrupted dose schedules with much larger dose levels were tolerated in mice and dogs. The minimal toxic dose of 40 mg/kg/week (120 mg/m²/week) was the same in both the 3-month and 6 month studies in mice. The minimal toxic dose of 3 mg/kg/week (60 mg/m²/week) was the same for both the 3-month and 6-month studies in dogs.

In special toxicity studies, the potential immunogenicity of gemcitabine was evaluated in guinea pigs. Gemcitabine alone or when combined ovalbumin did not induce immune responses for acute anaphylaxis and passive cutaneous anaphylaxis in guinea pigs. Gemcitabine did not induce hemolysis or serum flocculation in dog or monkey serum in vitro. In acute irritation study, 3 rabbits were exposed for 4 days to a moistened pad containing gemcitabine (concentration at 1 g/kg) placed over the shaved skin. Prior to deaths, two of three rabbits exhibited acute systemic toxicities similar to those observed in the acute single dose toxicity studies suggesting cutaneous absorption of drug. No local irritation was seen.

In a Segment I male fertility study, gemcitabine caused severe hypospermatogenesis, decreased fertility, and decreased implantations. In a Segment I female fertility study, gemcitabine had no effect on precoital, mating performance, or fertility. In Segment II reproductive studies, pregnant mice were given i.v. doses ranging from 0.05 to 1.5 mg/kg/day (0.15 to 4.5 mg/m²/day) gemcitabine during the gestation period. High dose gemcitabine administration resulted in maternal toxicities and fetal malformations such as cleft palate, digital and skeletal anomalies. About half of the mouse fetuses in the HD group were classified as runts. Pregnant rabbits received i.v. doses of gemcitabine ranging from 0.0015 to 0.1 mg/kg/day (0.0165 to 1.1 mg/m²/day) on gestation days 6 through 18. Gestational treatment with gemcitabine did not affect maternal body weight. Fetal visceral and skeletal malformations were observed and fetal weight, fetal viability, survival were reduced in the HD gemcitabine group. In a Segment III perinatal/postnatal study, i.v. doses of gemcitabine ranging from 0.05 to 1.5 mg/kg/day were given on gestation day 15 through postpartum day 20. Gemcitabine exposure produced decreases in maternal body weight and food consumption

only at 1.5 mg/kg/day, but reproduction parameters and progeny survival to weaning were not affected. Progeny weights were lower, developmental delays were observed and reduced physical activity was noted in the newborn whose mothers were exposed to HD gemcitabine in utero.

Gemcitabine at concentrations up to 5000 ug/plate was not mutagenic in Ames assay including *S. typhimurium* and *E. Coli*. Gemcitabine at concentrations up to 0.03 ug/ml (-S9) or 0.1 ug/ml (+S9) did not induce chromosomal aberrations in CHO cells. In adult rat hepatocytes, gemcitabine concentrations up to 1000 ug/ml did not induce unscheduled DNA synthesis. In vivo mammalian cell system, i.p. doses of 3.12-5 mg/kg gemcitabine did not produce an increase in the frequency of sister chromatid exchanges in chinese hamster cells. However, gemcitabine concentrations ranging from 0.001 to 0.06 ug/ml with or without S9 did induce forward mutation at thymidine kinase locus in L5178Y TK +/- mouse lymphoma cells. I.V. doses of gemcitabine ranging from 0.185 to 0.75 mg/kg daily for 2 days induced micronuclei in bone marrow cells of ICR mice.

Labeling Comments:

Labeling generally conforms to the format specified under CFR21. Part 201. Subpart B dated April 1, 1994. The proposed labeling describes the preclinical observations for the most part. However, the following revisions are requested:

1. Under Clinical Pharmacology on p. 2, delete _____ and the second paragraph should read " The cytotoxic effect of gemcitabine is attributed to a combination of two actions..... _____"

2. Under Clinical Pharmacology on p. 3, the last portion of the first paragraph should read: "In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of characteristics of a programmed cell death." Delete the following sentence

3. Under Precautions on p. 10, Carcinogenesis, Mutagenesis, Impairment of Fertility Section: The paragraph should be replace and should read:
 "**Carcinogenesis:** Long-term animal studies to evaluate the carcinogenic potential of Gemcitabine have not been conducted. **Mutagenesis:** Gemcitabine induced forward

 _____ (about 1/700 the human dose on a mg/m2 basis) _____
 moderate to severe hypospermatogenesis, decreased fertility and decreased implantation.

 _____ were observed at 1.5 mg/kg/day (about 1/200 the human dose on a mg/m2 basis) in

4. Under Pregnancy category section on p. 10: Pregnancy Category 'C' should be changed to 'D'. The beginning paragraph should read:

_____ can cause fetal harm when administered to a pregnant women. Gemcitabine is embryotoxic and causes fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day. _____

_____ Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays." There are no studies of Gemcitabine in pregnant women.....

5. Under Precaution section, information about possible dermal absorption should be included for handling of gemcitabine while in solution. In acute dermal irritation study, no dermal irritation was seen. However, 2/3 rabbits exhibited drug-related systemic toxicities (deaths, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.
6. Under Overdosage: The beginning paragraph should be changed to: " In mice and rats, lethal doses were about 500 mg/kg and 230 mg/kg given intravenously, respectively (about 1.5 times the usual human dose on a mg/m2 basis) with leg weakness, hair loss and clonic convulsions."

Recommendation:

This NDA is approvable from the pharmacologic/toxicologic aspect of application with revision of the labeling as listed in this review.

Draft Letters to the Sponsor:

Labeling generally conforms to the format specified under CFR21. Part 201. Subpart B dated April 1, 1994. The proposed labeling describes the preclinical observations for the most part. However, the following revisions are requested:

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3. Under Precautions on p. 10, Carcinogenesis, Mutagenesis, Impairment of Fertility Section: The paragraph should be replace and should read:

"Carcinogenesis: Long-term animal studies to evaluate the carcinogenic potential of _____ have not been conducted. Mutagenesis: _____ induced forward mutations in mouse lymphoma (L5178Y) cell assay: _____ and was clastogenic in an in vivo mouse micronucleus assay. Gemcitabine was negative when tested in Ames assay, sister

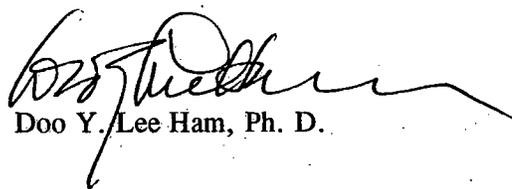
chromatid exchange assay in vivo, chromosomal aberration assay in vitro, and did not cause unscheduled DNA synthesis assay in vitro. **Impairment of Fertility:** Gemcitabine i.v. doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m2 basis) in malemice had an effect on male fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. _____ were observed at 1.5 mg/kg/day (about 1/200 the human dose on a mg/m2 basis) _____ embryoletality — observed at 0.25 mg/kg/ day (about 1/1300 the human dose on a mg/m2 basis) in mice.

- 4. Under Pregnancy category section on p. 10: Pregnancy Category 'C' should be changed to 'D'. The beginning paragraph should read:

_____ can cause fetal harm when administered to a pregnant women. Gemcitabine is embryotoxic and _____ fetal malformations (cleft palate, incomplete ossification) at doses of _____ (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits: _____ Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays." There are no studies of _____ in pregnant women.....

- 5. Under Precaution section, _____ irritation was seen. _____ hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

- 6. Under Overdosage: _____


Doo Y. Lee Ham, Ph. D.

cc: Original NDA 20-509
HFD-150/Division File
/LeeHam
/DeGeorge
/Schechter
/CSO


1/23/96

DYLH/WP
Revised on 10/16/95
Revised on 11/20/95
Revised on 1/4/96

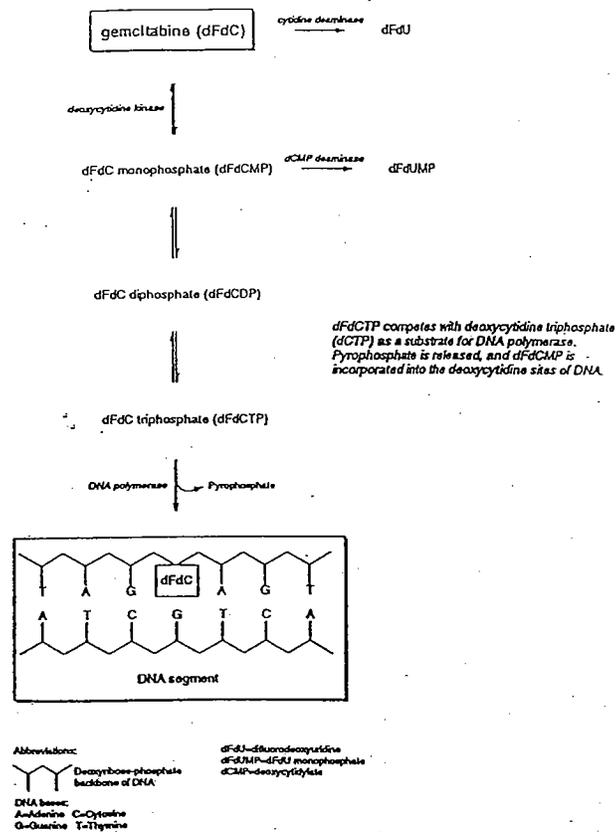
PHARMACOLOGY

1. Mechanism of Action:

Gemcitabine (2',2'-difluorodeoxycytidine; LY188011 HCl; dFdC) is a fluorinated cytarabine (Ara-C). The mechanism of action of gemcitabine is not fully understood. Like Ara-C, gemcitabine is a deoxycytidine analog that is cell cycle specific, killing cells at the early S-phase and blocking progression through the G1/S phase boundary.

Many studies indicated that the cytotoxic action of gemcitabine is due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. Gemcitabine is activated by deoxycytidine kinase (dCK) to diphosphate (dFdCDP) and triphosphate metabolite (dFdCTP). 1) dFdCDP inhibits ribonucleotide reductase. Inhibition of this enzyme causes a reduction of deoxycytidine triphosphate (dCTP), which results in increased phosphorylation of dFdC by dCK. 2) dFdCTP competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (this process is called masked chain termination).

Figure 2: Metabolic pathways of gemcitabine (dFdC) (adapted from references 5, 9, and 38)



As with most nucleoside analogues, gemcitabine and FIAU may have similar inhibitory effects on the DNA synthesis. However, the pathways of dFdC metabolism may differ from that of FIAU. evidence of hepatotoxicity was noted in the animal safety studies with gemcitabine.

TABLE 1. Cellular Metabolism and Mechanism of Action

Report No.	Parameter	Test System(s)	Results
A	Effects of dFdC and ara-C on cell cycle kinetics	CEM human leukemia cells LY5178 mouse leukemia cells	Gemcitabine exhibited cell phase specific, primarily killing cells undergoing at S-phase (DNA synthesis), and blocking progression through the G1/S phase boundary. Against CEM cells the minimum effects of dFdC was 0.02 ug/ml; whereas the minimal effective concentration for ara-C was 10-fold higher at 0.2 ug/ml. Gemcitabine was also more potent than ara-C in producing a G1/S phase block of LY5178K cells.
B	Determination of the intracellular metabolism of dFdC	Intact cells: CEM and K562 CHO, Molt-4 cells	Gemcitabine (dFdC) is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides.
C	Determination of the effect of dFdC and ara-C on nucleoside reductase	Intact cells: CEM and K562	dFdCDP inhibits ribonucleotide reductase. In contrast, ara-C, or its metabolites, have no effect on this enzyme. Inhibition of this enzyme causes a reduction of dCTP. Studies with variant L1210 indicated that ribonucleotide reductase is not the primary site of inhibition by dFdC.
D	Effect of dFdC on the deoxycytidine kinase(dCK)	Purified dCK from Molt-4 leukemia Intact cells: CEM and K562 cells	dCK is a key enzyme in the activation of dFdC. This enzyme is regulated by nucleoside triphosphate, in particular dCTP. Lowering dCTP conc. by dFdC's inhibition of ribonucleotide reductase causes an increase in phosphorylation of dFdC by dCK. These changes are not observed with ara-C.

TABLE 2. In Vitro Antitumor Activities Summary

Study No.	Parameter(s)	Cell Type(s)	Concentrations	Results
E	Inhibition of cell growth	CCRF-CEM human leukemia	10 to 10 ⁻⁴ ug/ml gemcitabine(dFdC)	Gemcitabine effectively inhibited growth. IC50 = 0.8 ng/ml
F	Comparison of the growth inhibitory action of dFdC and ara-C	Human leukemias: HL-60 Molt-3 RPMI-8392	ara-C: 0.1 to 10 uM gemcitabine: 0.01 to 1 uM	The growth inhibitory action of gemcitabine was both concentration and time dependent. IC50 value = 3.0 uM(RPMMI); 5.5 uM(HL-60); 10 uM (Molt-3) for gemcitabine. IC50 value = 26 nM(Mol-3); 47 nM(HL-60); 52 nM(RPMMI) for ara-C.
G	Comparison effect of dFdC and ara-C on clonogenicity	K562 human leukemia	dFdC: 10 uM ara-C: 10 uM	At 3 hr exposure, dFdC caused 50% cell kill IC50 = 10 uM for dFdC ara-C caused a 35% kill
H	Effect of dFdC on the growth of established rodent and human tumor cell lines	Rodent: C26-10 mouse colon Human: WiDr colon A2780 ovarian Ovcar-3 ovarian Ovcar-5 ovarian Panc-1 pancreatic 14C head and neck 22B head and neck	0.1 to 10 uM dFdC	The growth inhibitory effect of dFdC was time and concentration dependent. A comparable time dependence was observed in all cell lines, but the absolute IC50's varied greatly between the different cell lines. Gemcitabine was cytotoxic to all tumor cell lines. Inhibited the growth of the Ovcar-5, PANC-1. IC50 values ranged 2 to 25 nM.

TABLE 2 (Continued). In Vitro Antitumor Activities Summary

Study No.	Parameters	Cell Types(s)	Concentrations	Results
I.	Effect of dFdC on the clonogenicity of primary human solid tumor cells	Colorectal, breast, non-small cell lung, ovary, kidney, melanoma	2 to 200 ug/ml dFdC	The effect of dFdC on tumor colony formation was studied in 215 primary tumor samples. After 1 hr incubation, 94/215 samples were evaluable. The concentration-dependent increase in tumor cell growth inhibition was noted: 6/94 at 2 ug/ml, 13/94 at 20 ug/ml, and 33/94 at 200 ug/ml. A similar increase in tumor growth inhibition was seen using a continuous incubation (2 ug/ml: 0/14, 20 ug/ml: 1/14, 200 ug/ml: 7/14 specimens).
J.	Effect of dCyd on Ara-C and dFdC against normal bone marrow progenitor cells and cisplatin-sensitive and cisplatin-resistant ovarian carcinoma cells	2008 ovarian line (cisplatin sensitive) 2008/C13 ovarian line (cisplatin resistant)	Ara-C, 3 uM/ml dFdC, 1 uM/ml (4 hr exposure)	Ara-C and dFdC inhibited colony growth of the 2008/C13 greater than that of the 2008 ovarian carcinoma. Ara-C caused $90.8 \pm 1.6\%$ vs $76.1 \pm 3.6\%$ inhibition of 2008/C13 vs 2008 cells. dFdC caused greater inhibition of 2008/C13 vs 2008: $96.3 \pm 2.3\%$ vs $91.1 \pm 2.6\%$, respectively. Deoxycytidine reversed the cytotoxicity to normal human bone marrow cells, but did not alter the cytotoxicity to the ovarian carcinoma cells.
K	Anticancer agents against the human pancreatic carcinoma xenograft models	MIA PaCa-2, PANC-1 human pancreatic CD-1 nu/nu mice	dFdC: i.p. doses, 40, 80, 160 mg/kg, Q3D x 4	In general, in vivo antitumor activity roughly correlated with in vitro tumor cytotoxicity. Gemcitabine produced modest activity (69% inhibition in MIA PaCa and 79% inhibition in PANC-1).

TABLE 3. In Vivo Antitumor Activities Summary

Study No.	Parameter(s)	Tumor line Test Animal	Dose (mg/kg) Route, Schedule	Results
L	dFdC against a human xenograft models	Human head and neck carcinoma xenograft: HNX-HN HNX-LP HNX-14A HNX-14C HNX-22B All in NMRI nude mice	Six dose levels ranging from 2.5 to 240 mg/kg. i.p. qd x 5, or q3d x 4 or q7d x 2 (schedule used was determined by the dose level)	A MTD of dFdC was 120 mg/kg, q3d x 4. Q3D x 4 produced a significant antitumor effect (60-95% growth inhibition) in all 5 xenograft models. Other investigation of different schedules showed that treatment with a 3-day interval was superior to daily or weekly treatment.
M	The schedule and dose of dFdC on the antitumor efficacy	Soft tissue sarcomas Ovarian cancer xenografts NMRI nude mice	i.p. daily - 4 at 3.5 mg/kg; Q3d x 4 at 120 mg/kg; weekly x 2 at 240 mg/kg	In comparison with q3d schedule, the weekly and daily schedule was less effective. The weekly schedule resulted in >50% inhibition in 2/4 soft tips. sarcoma and 4/6 ovarian ca. The antitumor effect of dFdC was similar or even better than conventional cancer drugs.
N	Comparison of dFdC and ara-C against a panel of human carcinoma xenografts were compared	Human xenograft carcinoma models: CX-1, HC-1, GC3 and VR5 colon CALU-6, LX-1 & NCI-H460 lung, MX-1 mammary, HS766T, BxPc-3, PaCa-2 & Panc-1 pancreatic	dFdC: 1.25 to 160 mg/kg, i.p. days 1, 4, 7, 10 Ara-C: 2.5 to 80 mg/kg, i.p. daily x 10	At MTD, dFdC inhibited the growth of the HS-1, GC3, and VR5 colon ca. by 95-100%; the HS766T pancreatic and MX-1 mammary ca. by 80-94%; the CX-1 colon, CALU-6 lung, LX-1 lung, PaCa-2 and PANC-1 pancreatic ca. by 60-79%. It was inactive against the BxPc-3 pancreatic ca. and the NCI-H460 lung ca. In contrast, ara-C at MTD only inhibited the LX-1 lung ca. by 62% and the VRC5 colon ca. by 80%. It was not active against other tumors.

Summary of Pharmacology:

Gemcitabine, 2',2'-difluorodeoxycytidine (dFdC), is a fluorinated cytarabine. Like Ara-C, Gemcitabine is a nucleoside analog that is cell cycle specific, killing cells undergoing at S-phase (DNA synthesis), and blocking progression through the G1/S phase boundary. Gemcitabine is @10-fold more potent than Ara-C in producing a G1/S phase block in LY5178K leukemia cells.

Gemcitabine is activated intracellularly by deoxycytidine kinases, including nucleotide kinases, to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate (dFdCDP) inhibits ribonucleotide reductase (ara-C has no effect on this enzyme). Inhibition of this enzyme causes a reduction of dCTP, which will result in increased phosphorylation of dFdC by dCK which lead to inhibition of DNA synthesis.

The *in vitro* cytotoxic action and antitumor activity of gemcitabine at concentrations ranging 0.01 μ M to 10 μ M is seen in CCRF-CEM, HL-60, Molt-3 and RPMI-8392 human leukemias. At equivalent doses of 10 μ M, gemcitabine killed 50% of cells at 3 hr exposure compared to 35% kill at 5 hr by ara-C in K562 human leukemia. Gemcitabine concentrations up to 10 μ M inhibited the clonogenicity of rodent (mouse C26-10) colon carcinoma and established human tumor cell lines (WiDr colon, ovarian (A2780, ovcar-3, ovcar-5), PANC-1 pancreatic, and 14C and 22B head and neck carcinoma). The antitumor activity of gemcitabine is demonstrated against a variety of primary human solid tumor cells at concentration of 2-200 μ g/ml in the *in vitro* capillary soft agar cloning system. Gemcitabine and Ara-C against cisplatin-resistant (2008/C13) and cisplatin-sensitive (2008) ovarian carcinomas were compared *in vitro*. By comparison, the cisplatin-resistant 2008/C13 ovarian carcinoma was 3 times more sensitive to gemcitabine.

The antitumor activity of gemcitabine is seen in a broad spectrum of human tumors grown as xenografts including MIA PaCa-2 and PANC-1 human pancreatic carcinomas in nude mice. *In vitro*, the IC₅₀ values of gemcitabine were 0.019 μ g/ml in PaCa-2, 0.015 μ g/ml in PANC-1, and 0.007 μ g/ml in CCRF-CEM cells. CCRF-CEM leukemia cells are more sensitive than PaCa-2 and PANC-1 pancreatic carcinomas cells. *In vivo*, gemcitabine produced modest activity (69% inhibition in MIA PaCa and 76% inhibition in PANC-1) when given *i.p.* dose of 80 mg/kg on Q3D for 4 treatments. *In vivo* antitumor activity roughly correlated with *in vitro* cytotoxicity.

In vivo data also demonstrated that the antitumor activity of gemcitabine is schedule dependent. Schedule dependency of antitumor activity of gemcitabine was demonstrated in NMRI nude mice. The Q3D x 4 schedule was found to be superior to weekly or daily injections with significant antitumor effect observed in SCCHN tumor lines.

The antitumor activity of gemcitabine was compared with Ara-C in a panel of human (breast, colon, lung, and pancreatic) xenograft models. Gemcitabine inhibited the growth of the CX-1, HC-1, GC3 and VRC5 colon carcinomas by 92-99%. Ara-C marginally inhibited the growth of the HC-1 colon (52%) and LX-1 lung tumors (62%) only. Gemcitabine demonstrated good antitumor activity against the MX-1 breast and CALU-6 and LX-1 non small cell lung models. In pancreatic carcinoma xenograft models including those that are resistant to conventional chemotherapy, gemcitabine inhibited the growth in the Hs766T, PaCa-2 and PANC-1 pancreatic carcinomas by 82, 69, 76%, respectively. The BxPc-3 pancreatic carcinoma was resistant to gemcitabine.

II. PHARMACOKINETICS:

1. Single Dose Pharmacokinetic Studies: (vol. 1.34 & 1.35)

Plasma pharmacokinetics of LY188011 and its deaminated metabolite, 198791, in B6C3F1 mice administered a single intravenous dose of 20 mg/kg of 14C-LY188011 HCl, ADME Study Report 7

Plasma pharmacokinetics of LY188011 and its metabolite 198791 in Fischer 344 rats following a single intravenous administration of 10 mg/kg of 14C-LY188011 HCl, ADME Study Report 21

Plasma pharmacokinetics of LY188011 and its metabolite, 198791 in Beagle dogs following a single intravenous administration of 5 mg/kg of 14C-LY188011 (Study DO9986), ADME Study Report 27

Summary of the plasma pharmacokinetics of gemcitabine in B6C3F1 mice, Fischer344 rats, beagle dogs and man after intravenous administration

<u>Parameter</u>	<u>Mouse</u>	<u>Rat</u>	<u>Dog</u>	<u>Man</u>
Dose mg/kg(mg/m ²)	20 (60)	10 (60)	3 (60)	(1000)
Frequency, Route	Single,IV bolus	Single,IV bolus	Single,IV bolus	Single,IV infusion
C _{max} (ug/ml)				
LY188011	40.78	9.08	4.05±0.38	18.2
LY198791	3.25	0.22	1.96±0.18	39.3
T _{max} (hr)				
LY188011	0.017	0.017	0.033-0.33	0.017
LY198791	0.167-0.25	4-6	2-4	0.05-0.25
AUC(ug.hr/ml)				
LY188011	9.27	30.36	8.07±1.00	8.2
LY198791	6.79	3.21	25.43±5.39	
Plasma T _{1/2} (hr)				
LY188011	0.28(α)	2.14(α) 8.81(β)	1.38(α) 1.76(β)	0.28(β)
LY198791	NC	2.38(β)	NC	65.3(β)
Correlation coefficient				
α	0.925	0.996	0.967	
β	NC	0.871	0.997	

LY188011 = Gemcitabine

LY198791 = Uracil metabolite

NC = not calculated

In plasma pharmacokinetic studies, gemcitabine is rapidly deaminated in the mouse with a uracil metabolite ($C_{max}=3.25$ ug/ml) measurable within 2 minutes post dosing.

After an i.v. dose to rats, gemcitabine disappeared from the plasma with an initial half-life of 2.14 hr and a terminal half-life of 8.81 hr. Peak gemcitabine concentration was 9.08 ug/ml at 0.017 hr. Peak plasma concentration of the uracil metabolite was 0.22 ug/ml seen 4 to 6 hr post-dose. In the rat, plasma AUCs for gemcitabine and the uracil metabolite were 30.36 ug.hr/ml and 3.21 ug.hr/ml (Plasma AUC of the uracil metabolite 11% of the plasma AUC of the parent compound).

In dog study, gemcitabine was eliminated from the plasma with an initial half-life of 1.38 ± 0.16 hr and a terminal half-life of 1.76 ± 0.08 hr after a dose of 3 mg/kg i.v to dogs. Peak gemcitabine concentration of 4.05 ± 0.38 ug/ml was seen at 0.17 hr and C_{max} of the uracil metabolite was 1.96 ± 0.18 ug/ml and occurred at 2 to 4 hr post-dose. Gemcitabine AUC in dog was 8.07 ug.hr/ml vs 25.43 ug.hr/ml for the metabolite indicating more rapid deamination in the dog as compared to the rat.

2. Tissue Distribution Studies: (vol. 1.35)

Tissue Concentrations of Radioactivity in B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14 -C-LY188011 Hydrochloride, ADME Study Report 11

Tissue Concentrations of Radioactivity in Tumor Bearing B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14 -C-LY188011 Hydrochloride, ADME Study Report 12

Tissue Concentrations of Radioactivity in Fischer 344 Rats Following a Single Intravenous Administration of 10 mg/kg of 14 -C-LY188011 Hydrochloride, ADME Study Report 24

Tissue Concentrations of Radioactivity in Mice Following a Single Intravenous Administration of 20 mg/kg of 14 -C-LY188011 Hydrochloride, ADME Study Report 11:

Mouse:

A tissue distribution study was conducted in male B6C3F1 mice following a single i.v. dose of 20 mg/kg 14 C-LY188011. Selected tissue samples were collected at 1, 5, 10, 20, 30, 60, and 1440 minutes to quantitate for radiolabeled contents by combustion and liquid scintillation counting.

Radioactivity was rapidly distributed to tissues with peak concentration reached within 1-30 minutes in all examined tissues. The highest concentrations of radioactivity, based on AUCs were in the spleen (4.5X the plasma), thymus (2.6X), testicles (2.5X), kidney (2.3X), femur (1.7X), small intestines (1.6X), and lymph nodes (1.5X). However, peak concentration in the testicles (22.9 ug.eq.hr/g) were not reached until nearly 3 hrs after dosing. The tissue half-lives of radioactivity ranged from 0.75 to 2.96 hr as shown in the table below.

Tissue distribution of ¹⁴C-radiolabel in mice administered a single intravenous dose of 20 mg/kg of gemcitabine

Tissue	AUC (0.0167- 24 hr) μg eq-hr/g	T _{max} min	C _{max} μg eq/g	Half-Life	
				Ho- urs	Time Range* hr
Blood	28.58	1.0	39.37	1.56	0.5-4
Plasma	32.03	1.0	38.74	1.58	0.5-4
Spleen	126.39	30.0	50.19	1.40	0.5-6
Kidney	65.51	1.0	90.58	1.62	0.5-6
Liver	35.04	1.0	44.81	1.59	0.5-6
Pancreas	46.01	1.0	32.03	1.90	0.5-6
Lung	34.11	1.0	33.74	1.50	0.33-4
Salivary gland	28.28	1.0	28.81	1.38	0.5-4
Thymus	76.12	10.0	24.13	1.66	1.0-6
Testicles	74.29	30.0	22.99	2.96	1.0-6
Stomach	32.87	1.0	25.42	1.98	0.5-6
Small intestine	45.25	1.0	25.48	1.98	0.33-4
Muscle	35.84	1.0	20.35	2.95	0.5-6
Heart	38.95	1.0	47.08	1.92	0.5-6
Femur	47.48	30.0	15.95	1.55	0.5-6
Adrenals	18.42	1.0	16.06	0.75	0.17-2
Skin (ears)	37.97	10.0	16.63	1.68	0.5-6
Fat	4.96	1.0	2.13	2.20	0.5-4
Lymph nodes	43.03	10.0	20.03	1.32	1.0-6
Brain	18.23	30.0	4.92	1.80	1.0-6
Spinal cord	15.20	30.0	4.22	1.61	1.0-6
Sciatic nerve	9.68	10.0	4.16	1.78	0.5-4
Eyes	31.59	30.0	8.71	1.58	0.02-0.33

* Time over which half-life was calculated.

Tissue Concentrations of Radioactivity in Tumor Bearing Mice Following Single Intravenous Administration of 20 mg/kg of ¹⁴C-LY188011 Hydrochloride, ADME Study Report 12:

Mouse:

Female tumor (X-5565) bearing B6C3F1 mice were administered an i.v. dose of 20 mg/kg ¹⁴C-LY188011. Selected tissue samples were collected at a single time point (30 min) to determine radiolabeled content.

The radioactivity was rapidly distributed to tissues at tissue concentrations comparable to that of non-tumor bearing mice. The X-5565 tumor had high concentrations of radioactivity. Tissues containing the highest concentrations of radioactivity were spleen, tumor, thymus, kidney, and lymph nodes as shown in the following table.

Distribution of Radioequivalent ¹⁴C-LY188011 in Tumor (X-5563) Bearing B6C3F1 Female Mice 30 Minutes After a Single Intravenous Dose of 20 mg/kg of ¹⁴C-LY188011 Hydrochloride

Tissue	Mean (±SD)
Spleen	52.18 (20.75)
Kidney	30.09 (0.76)
Liver	15.07 (1.21)
Pancreas	12.04 (1.10)
Lung	14.09 (1.85)
Thymus	23.86 (1.85)
Tumor A*	33.43 (4.67)
Tumor B	40.32 (3.42)
Lymph Node (Brachial)	39.10 (2.07)
Lymph Node (Mandibular)	47.09 (2.99)
Muscle	10.66 (0.42)
Heart	13.28 (0.66)
Skin (Ears)	13.43 (1.52)
Brain	4.64 (0.11)
Whole Blood	9.69 (0.39)
Plasma	10.42 (0.28)

*Two sections of the same tumor.

Units are expressed in μg ¹⁴C-equivalent LY188011/gram wet tissue or ml of plasma.

Tissue Concentrations of Radioactivity in Fischer 344 Rats Following a Single Intravenous Administration of 10 mg/kg of ¹⁴C-LY188011 Hydrochloride, ADME Study Report 24:

Rats:

A tissue distribution study was conducted in male rats following a single i.v. dose of ¹⁴C-LY188011 HCl (10 mg/kg) to quantitate radiolabel concentrations in blood. Selected tissue samples were collected at 1, 5, 10, 20, 30 min up to 24 hr.

Concentrations of gemcitabine related radioactivity were determined and tissue pharmacokinetic parameters are shown in the following table. The highest concentrations of radiolabel were in the thymus, kidney, lymph nodes, and spleen (similar to mice). Tissue half-lives of radioactivity ranged from 1.93 to 5.68 hr.

Tissue distribution of ¹⁴C-radiolabel in rats administered a single intravenous dose of 10 mg/kg of gemcitabine

Tissue	AUC (0.0167- 24 hr) μg eq·hr/g	T _{max} min	C _{max} μg eq/g	Half-Life	
				Ho- urs	Time Range ^a hr
Blood	31.66	1.0	19.48	1.47	0.1-4
Plasma	34.27	1.0	20.03	1.68	0.1-4
Spleen	65.66	30.0	11.50	3.18	1.0-6
Kidney	99.82	5.0	36.79	1.93	0.5-4
Liver	46.46	5.0	11.38	2.54	0.5-6
Pancreas	51.52	5.0	11.77	3.04	0.5-6
Lung	44.67	1.0	17.72	2.34	0.5-6
Salivary gland	40.74	5.0	14.68	2.44	0.5-4
Thymus	130.64	60.0	15.91	5.20	1.0-8
Testicles	50.30	30.0	9.50	2.32	0.5-6
Stomach	34.88	5.0	7.78	2.40	0.5-8
Small intestine	36.78	5.0	8.29	2.41	0.5-6
Muscle	49.98	5.0	11.10	3.05	0.5-6
Heart	53.40	1.0	30.05	2.17	0.5-6
Femur	30.34	5.0	5.70	2.48	1.0-6
Adrenals	35.13	1.0	11.51	2.05	0.5-6
Skin (ears)	46.20	30.0	9.20	3.72	0.5-6
Fat	5.60	60.0	0.87	3.40	1.0-8
Lymph nodes	66.01	20.0	11.63	3.67	0.5-6
Brain	11.93	120.0	1.28	5.68	4.0-16
Spinal cord	14.68	1.0	2.85	3.03	1.0-8
Sciatic nerve	16.38	60.0	3.05	2.52	2.0-6
Eyes	20.58	1.0	4.16	2.78	1.0-6

Evaluation of the In Vitro Protein Binding of ¹⁴C-LY188011 in Mouse, Rat, Dog, Monkey and Human Plasma, ADME Study Report 18: (vol. 1.35)

In vitro protein binding of ¹⁴C-LY188011 with and without tetrahyrouridine was determined using a Centrifree Micropartition System (Amicon). Mouse plasma was spiked with [2-¹⁴C]-LY188011 to final concentrations of 40, 4, and 0.1 ug/ml, rat plasma was spiked to final concentrations of 20, 2, and 0.1 ug/ml, and dog plasma was spiked similarly to final concentrations of 10, 1, and 0.1 ug/ml. In all assays binding was determined in 99% plasma. Triplicate aliquots of each concentrations were analyzed by liquid scintillation counting.

The concentration of protein-bound gemcitabine was found to be negligible at all dose levels and in all species tested. Free drug estimated from radioactivity present in the ultrafiltrate, represents a range of 95.5 to 102.7% of the radioactivity spiked into plasma.

4. Metabolism and Metabolites:

(vol. 1.36)

Urinary Metabolites of LY188011 Isolated From B6C3F1 Mice Following a Single Intravenous Administration of 20 mg/kg of 14-C-LY188011 Hydrochloride, ADME Study Report 13

Urinary Metabolites of LY188011 Isolated From Fischer 344 Rats Following a Single Intravenous Administration of 10 mg/kg of 14-C-LY188011 Hydrochloride, ADME Study Report 25

Urinary Metabolites of 14-C-LY188011 Isolated from Beagle Dogs Following a Single Intravenous Administration of 5 mg/kg of 14-C-LY188011 Hydrochloride, ADME Study Report 29

_____ were administered 20 mg/kg i.v. dose of [2-14C]-LY188011 via tail vein and group housed in a metabolism cage. Urine and feces samples were collected at 6, 24, 48, 72, 96, and 120 hr postdosing. _____ were administered 10 mg/kg i.v. dose of [2-14C]-LY188011 via tail vein and housed individually in metabolism cages. Urine and feces samples were collected at 6, 24, 48, 72, 96, and 120 hrs postdosing. Four beagle dogs (2♂, 2♀) were administered 5 mg/kg i.v. dose of [2-14C]-LY188011 via cephalic vein and individually housed in metabolism cages. Urine and feces samples were collected at 12, 48, and 72 hrs postdosing. Urinary metabolites and hydrolysis products were separated and analyzed by HPLC method.

In all three species gemcitabine was metabolized to the uracil metabolite. More extensive deamination occurred in the dog and mouse. Gemcitabine, uracil metabolite, gemcitabine glucuronide and uracil metabolite glucuronide were identified.

Urinary metabolite profiles of [¹⁴C]gemcitabine in B6C3F1 mice, Fischer 344 rats, and beagle dogs after intravenous administration

	Mouse	Rat	Dog
Average % of total dose in urine			
Gemcitabine	7.9	67.5	4.8
Gemcitamine glucuronide	5.9	0.7	0.8
Uracil metabolite	58.3	16.6	70.6
Glucuronide of uracil metabolite	12.9	0.9	6.5
Total identified	85.0	85.7	82.7
% Total dose in urine	87.9	87.1	84.9

Metabolite profiles in the urine were qualitatively, but not quantitatively, similar in mice, rats and dogs. Unchanged gemcitabine, the uracil metabolite, and glucuronides of gemcitabine and the uracil metabolites were found in mouse, rat and dog urine. The dog and mouse had similar percentages in the uracil metabolite in the urine. In rat, less extensive metabolism of gemcitabine to the uracil metabolite occurs with low urinary excretion of uracil metabolite. No evidence to suggest cleavage of the sugar moiety from cytosine or uracil was found.

Further identification of glucuronidated conjugates of gemcitabine and the uracil metabolite was conducted by comparison of the unhydrolyzed and β -glucuronidase-treated urine samples as in the figure 4. Evidence of glucuronidation was a decrease in the intensity of one peak (the glucuronidated molecule) with a subsequent increase in another peak (the aglycone) in the TLC analysis. Decreases and increases were determined relative to the unhydrolyzed samples.

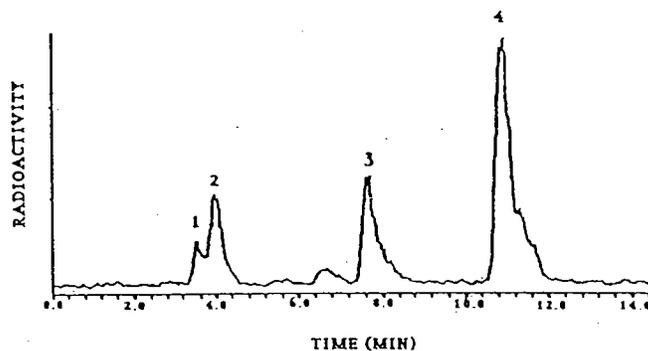


FIG. 4. Radiochromatogram of 0-24 hr mouse urine after intravenous administration of 20 mg/kg gemcitabine.

Peak 1, gemcitabine glucuronide; peak 2, glucuronide of the uracil metabolite of gemcitabine; peak 3, gemcitabine; and peak 4, uracil metabolite of gemcitabine.

Enzyme Induction Study in Rats:

(vol. 1.36)

After gemcitabine i.v. dose of 1 mg/kg, saline or phenobarbital sodium 100 mg/kg, p.o. to non-fasted males, the body weight, liver weight, liver microsomal protein content, cytochrome P-450 content, and other enzyme activities were determined using a spectrophotometer

Table 1 Effect of treatment with LY188011 or Phenobarbital for 5 days on the hepatic drug-metabolizing enzymes of male rats

Parameter	Vehicle (2ml/kg/day:i.v.)	LY188011 (1mg/kg/day:i.v.)	Phenobarbital sodium (100mg/kg/day:p.o.)
Body weight (g)	193 ± 4 (1.00)	186 ± 3 (0.96)	197 ± 2 (1.02)
Liver weight (g)	7.11 ± 0.21 (1.00)	6.97 ± 0.25 (0.98)	9.94 ± 0.22 (1.40)‡
Liver weight/body weight (%)	3.71 ± 0.06 (1.00)	3.73 ± 0.09 (1.01)	5.04 ± 0.08 (1.36)‡
Microsomal protein content (mg/g liver)	40.56 ± 1.55 (1.00)	45.95 ± 3.14 (1.13)	57.70 ± 4.38 (1.42)*
	289 ± 17 (1.00)	319 ± 22 (1.10)	573 ± 45 (1.98)‡
Aminopyrine N-demethylase activity (nmol/min/mg protein)	7.12 ± 0.28 (1.00)	6.12 ± 0.33 (0.86)*	14.19 ± 0.87 (1.99)‡
(nmol/min/g liver)	287 ± 10 (1.00)	280 ± 22 (0.98)	807 ± 34 (2.81)‡
(µmol/min/liver)	2.05 ± 0.11 (1.00)	1.95 ± 0.17 (0.95)	8.04 ± 0.46 (3.92)‡
Aniline hydroxylase activity (nmol/min/mg protein)	0.368 ± 0.014 (1.00)	0.321 ± 0.019 (0.87)	0.544 ± 0.052 (1.48)*
(nmol/min/g liver)	14.84 ± 0.29 (1.00)	14.53 ± 0.44 (0.98)	30.64 ± 1.72 (2.06)‡
(nmol/min/liver)	106 ± 4 (1.00)	101 ± 1 (0.95)	306 ± 22 (2.89)‡
UDPG transferase activity (nmol/min/mg protein)	0.515 ± 0.076 (1.00)	0.415 ± 0.017 (0.81)	0.713 ± 0.058 (1.38)‡
(nmol/min/g liver)	21.1 ± 3.7 (1.00)	19.0 ± 1.2 (0.90)	43.9 ± 0.8 (2.08)‡
(nmol/min/liver)	150 ± 26 (1.00)	132 ± 5 (0.88)	436 ± 11 (2.91)‡
Cytochrome P-450 content (nmol/mg protein)	0.381 ± 0.013 (1.00)	0.371 ± 0.014 (0.97)	1.066 ± 0.082 (2.80)‡
(nmol/g liver)	15.4 ± 0.6 (1.00)	17.0 ± 1.3 (1.10)	61.4 ± 5.8 (4.00)‡
(nmol/liver)	110 ± 6 (1.00)	118 ± 9 (1.07)	608 ± 48 (5.51)‡

Data are expressed as the mean values ± S.E. of five animals.
values in parentheses are expressed as the ratio of drug treatment relative to vehicle.
Significantly different from value of vehicle : *:(P<0.05). *(P<0.01). ‡:(P<0.001)

Results: After gemcitabine treatment, no significant differences were observed in the body weight (wt), liver weight and liver weight/body weight ratio and liver microsomal protein content. In hepatic drug metabolizing enzyme activity, gemcitabine tended to decrease aniline hydroxylase, UDPG transferase and aminopyrine activities whereas phenobarbital groups increased these enzyme activities. Gemcitabine had no activity in the cytochrome P-450 content in F344 rat.

5. Excretion Studies:

(vol. 1.37)

Elimination of Radioactivity from B6C3F1 Mice Following Intravenous Administration of 20 mg/kg of LY188011 HCl, ADME Study Report 16

Elimination of Radioactivity from Fischer 344 Rats Following Intravenous Administration of 10 mg/kg of ¹⁴C-LY188011 Hydrochloride, ADME Study Report 26

Elimination of Radioactivity from Beagle Dogs Following Intravenous Administration of 5 mg/kg of ¹⁴C-LY188011 Hydrochloride, ADME Study Report 30

Mice, rats and dogs:

After male mice, male rats and dogs (♂ & ♀) were given a single i.v. dose of 20 mg/kg, 10 and 5 mg/kg ¹⁴C-LY188011 HCl, respectively, urine (6-120 hrs) and feces samples (24-120 hrs) were collected and analyzed by Liquid Scintillation counting. Results are summarized in the table below.

Excretion of radioactivity in urine and feces of B6C3F1 mice, Fischer 344 rats, and beagle dogs following a single intravenous administration of [¹⁴C]gemcitabine

Time	Excretion Method	Mouse	Rat	Dog
<i>hr</i>				
24	Urine	86.28	77.91 ± 5.12	75.50 ± 4.30
	Feces	0.64	1.43 ± 0.44	0.80 ± 1.40
48	Urine	0.83	4.92 ± 1.29	4.10 ± 4.30
	Feces	0.59	1.21 ± 0.57	1.00 ± 0.70
72	Urine	0.47	1.06 ± 0.42	4.20 ± 4.20
	Feces	0.11	0.45 ± 0.04	1.70 ± 1.90
96	Urine	0.29	0.36 ± 0.11	NS ^a
	Feces	0.09	0.23 ± 0.24	NS
120	Urine	0.01	0.15 ± 0.10	NS
	Feces	0.01	0.58 ± 0.03	NS
Total	Urine	87.87	84.40 ± 5.90	84.90 ± 5.70
	Feces	1.44	3.37 ± 1.18	3.50 ± 1.00

^a NS, no sample collected.

Values represent the average recoveries from four male rats receiving 10 mg/kg iv, two male and two female dogs receiving 5 mg/kg iv, or the pooled samples of nine male mice administered 20 mg/kg iv. Values are expressed as percentage of the total dose excreted (±SD).

The main route of excretion in all three species was urinary, fecal elimination was minimal. The vast majority of metabolite was recovered in the urine within the first 24 hr after administration with 86.3, 77.9, and 75.5% found in the first 24-hr sample from the mouse, rat, and dog, respectively. Fecal elimination to the total was minimal, accounting for 1.4, 3.4, and 3.5% of the total dose administered to the mouse, rat, and dog, respectively.

Summary of Pharmacokinetics:

Single i.v. dose pharmacokinetics studies of gemcitabine (LY188011 HCl) have been conducted in mice, rats and dogs. After intravenous administration, gemcitabine rapidly disappeared from plasma in mice, rats, dogs and man. Interspecies analysis of pharmacokinetic based on i.v. bolus administration is as below:

	<u>Species</u>	<u>AUC Unit</u>	<u>Cmax Unit</u>
Parent	mouse	0.1545	0.67
	rat	0.506	0.15
	dog	0.135	0.068
	man	0.082	0.018
Metabolite	mouse	0.113	0.54
	rat	0.0535	0.0036
	dog	0.42	0.032
	man	not calculated	0.0393

On a mg/m² basis gemcitabine AUC for the rat is the greatest followed by mouse, dog and man. Since the rat is the most sensitive species in toxicity studies, the rank orders for Cmax and AUC suggest gemcitabine toxicity is more related to AUC than to Cmax.

Tissue concentrations of [¹⁴C]-gemcitabine radioactivity administered intravenously in the rat and mouse indicated that gemcitabine was rapidly distributed throughout the body within 1-30 min. The half-lives of radioactivity in tissues in both the rat and mouse ranged 1.9- 5.7 hr and 0.8-3.0 hr, respectively. In both species the highest AUCs of radiolabeled drug were found in the spleen, thymus, kidney, and lymph nodes and the lowest AUCs in fat and neural tissues. The target organs in toxicity studies included spleen, thymus and lymph node (tissues with higher deposition of radiolabel). Tissue distribution of radiolabel in X-5565 tumor-bearing mice and in non-tumor bearing mice were similar. Although high concentrations of radioactivity were detected in the tumor tissue of the tumor bearing mice.

In vitro gemcitabine plasma protein binding was determined to be negligible in mouse, rat, dog, monkey and human.

Urinary metabolic profiles were similar in all species. The major metabolite of gemcitabine is the uracil metabolite via deamination in mouse, rat, dog and man. Deamination in the mouse (66.3%) and dog (89.3%) was more extensive than in the rat (12.5%), probably due to differential expression and activity of species-dependent cytidine deaminase. The rat produced the least amount of inactive metabolite, consistent with the fact gemcitabine produces the most toxicity in the rat due to decreased deaminase concentration. Unchanged gemcitabine, the uracil metabolite, gemcitabine glucuronide, and the uracil metabolite glucuronide were identified in the urine in all species.

The major route of excretion of radiolabel in mouse, rat and dog was urine. Urinary excretion ranged 76-86% in the 24 hr. Fecal elimination was 1.4-3.5% in these species.

III. TOXICOLOGY:

The following toxicity studies contained QA and GLP statements except the first mouse study (study No. M05991).

A. The acute toxicity of compound _____ an impurity of Gemcitabine given intravenously to CD-1 mice, Study No. M05991: (vol. 1.18)

A Non-GLP study with only a summary statement included.

Acute toxicity studies were conducted to compare the toxicity of compound _____ (the _____ of gemcitabine) to the parent compound LY188011 HCl in adult CD-1 mice. Fasted CD-1 mice (5/sex/group) received a single i.v. dose of 500 mg _____ (Lot V26-2BV-40C)/kg (1500 mg/m²) at a dose concentration of 23 mg _____. The 500 mg/kg represents the maximum possible dose and highest dose volume based on the physical characteristics of the test article for intravenous dose in mice (25 ml/kg). All animals were observed for 2 weeks for mortality and signs of toxicity.

Results:

In both studies, all animals survived the test periods. The only observation was hypoactivity. Animals were normal within 3 hrs post-dosing and gained weight during the observation period. There was no notable difference in the acute toxicity of compound _____ as compared to the parent LY188011 HCl when administered intravenously at a dose of 500 mg/kg to CD-1 mice. The median lethal dose of compound _____ is > 500 mg/kg.

B. The acute toxicity of compound _____ an impurity of Gemcitabine given intraperitoneally to Fischer 344 rats, Study No. R27790: (vol. 1.17)

Fasted Fischer344 rats (5/sex/group, 8-9 weeks old) received a single intraperitoneal dose of either 0, 90, 225 or 500 mg _____. Lot V95-5ER-206B was used for this study. All animals were observed for 2 weeks for mortality and signs of toxicity.

Measurements and observations:

Daily: survival & clinical signs (hourly for 7 hrs, and for 2 weeks)
 weekly: body weight
 Termination: gross necropsy

Results:

All the animals died at 500 mg/kg dose and 3/5♂ and 4/5♀ died at 225 mg/kg dose within 8-10 days. Median lethal dose was calculated as 214 mg/kg(♂) and 174 mg/kg(♀).

Clinical signs included animal soiling, hunched posture, excessive shedding of hair, hypoactivity, piloerection, soft stools [days 5-6(♂) & 4-7(♀)], poor grooming, emaciation, salivation, lethargy, and lack of feces [day(s) 8(♂) & 8-15(♀)]. Severity/incidence were dose related. No toxic signs were observed in the low and vehicle control groups. Males and females receiving either 225 or 500 mg dose had a significant mean body weight loss (23 and 28% or 39 and 34%, respectively) at day 8. On day 15, males and females with 225 mg had 12% and 34% depression in mean body weight gain. No significant weight losses were observed in the low dose and controls.

Gross lesions included red foci in lungs, pale liver, small thymus and spleen, enlarged lymph nodes, and enlarged testes in mid and high dose groups.

C. The Acute toxicity of compound _____ the major degradation product of Gemcitabine HCl given intravenously to Fischer 344 rats, Study No. R19491: (vol. 1.18)

Fasted female Fischer344 rats (5/group, 9-10 weeks old) received a single intravenous dose of either 45, 90, 180, or 330 mg compound _____ in saline solution. Vehicle control received a single i.v. dose of 0.9% NaCl injection, USP, equivalent to the maximum volume test solution administered (22 ml/kg). All animals were observed for 2 weeks. Lot L67-6AC-114 was used.

Measurement and Observations:

Daily: survival & clinical signs (hourly for 7 hrs, and for 2 weeks)
weekly: body weight
Termination: gross necropsy

Results:

No deaths occurred among treated or vehicle control animals. No signs of toxicity were observed. Mean body weight gain of treated animals were similar to that of control animals on days 8 and 15. No drug-related lesions were found. The median lethal dose of compound _____ is > 330 mg/kg when given intravenously to female rats.

D. An acute toxicity study of Gemcitabine HCl(LY188011; compound _____ given by bolus intravenous administration to dogs, Study No. D02791: (vol. 1.17)

Beagle dogs (1/sex/group, 8 to 10 months) were used for two consecutive treatments (Phase I and II). Each pair received a single i.v. dose of 3 or 12 mg gemcitabine/kg on day 1 for Phase I and a single i.v. dose of 18 and 24 mg gemcitabine/kg on day 15 for Phase II. Lot G76-9W-073: _____ was used. No vehicle (phosphate buffered saline) control group was used. Animals were observed for 28 days.

Measurement and Observations:

Daily: survival and clinical signs (for 3 hours and thereafter daily)
Weekly: body weight, hematology, clinical chemistry
Termination: no necropsy

Results:

All dogs survived until study termination. During Phase I, all dogs appeared normal with few occurrences of soft/mucoid stools on days 5 and 11 in females given 12 mg gemcitabine. No other treatment-related clinical signs were observed. During Phase II, all dogs appeared normal except for soft stools on day 18 in female given 18 mg/kg gemcitabine and male given 24 mg/kg gemcitabine.

No treatment-related changes in body weight and food consumption occurred during the study. A pronounced decreases in neutrophil counts (approximately 50% of pretreatment values) were observed on day 4 post-dose. Reversible neutropenia occurred in dogs at each dose level. No other hematologic parameters were affected. Minimal increases in AST values (23%) were observed in 3/4 dogs during Phase II of the study. No necropsy was performed.

E. A Chronic toxicity study of Gemcitabine HCl given intraperitoneally to CD-1 mice for 6 months with a 2-month reversibility study, Study No. M25589 and M25689:
(vol. 1.19)

Chronic effects of i.p. administration for 6 month treatment followed a 2 month recovery period of LY188011 were studied. Lot CT-8974-7A and CT-8975-9C were used for this study. CD-1 mice (20/sex/group, 22-28 g, 5-6 weeks old) were given i.p. doses of 0 (PBS), 0.5, 5 or 40 mg/kg for 2, 7, 2 or 1 time each week, respectively (Study M25589, See the mortality table). Similarly, mice (10 sex/group) were given LY188011 for 6 months followed by a 2-month recovery period (Study M2568).

Measurements and Observations:

Daily: survival, clinical signs

Weekly: body weight and food consumption

183 and 240 days: hematology and clinical chemistry

Termination: gross/histopathology

Results:

Mortality/Clinical signs:

<u>Treatment Group</u>	<u>Dose (mg/kg)</u>	<u>Schedule</u>	<u>Study 25589</u>		<u>Study 25689</u>	
			<u>Mortality</u>	<u>Mortality</u>	<u>Mortality</u>	<u>Mortality</u>
Control	0	Biweekly	♂	♀	♂	♀
LD	0.5	Daily	-	1/20	1/10	2/10
MD	5	Biweekly	3/20	3/20	-	-
HD	40	Weekly	-	1/20	-	1/10
			1/20	-	-	2/10

In a 6 month treatment group, 1/20♂ at HD, 1/20♀ at MD, 3/20♂ and 3/20♀ at LD and 1/20♀ at control died whereas the mortality in the reversible phase, the deaths were 2/10♀ at HD, 1/10♀ at MD, no deaths at LD and 1/10♂ and 2/10♀ died at control group. No significant changes in clinical signs and food consumption were observed. A slight incidence of abdominal swelling was noted in mice treated LD daily near the end of the treatment phase in both studies.

Body weight/food consumption:

Male and female mice receiving the LD had significantly lower mean body weights (8.3%♂ & 8.9%♀ (M25589) and 11.1%♂ & 9.7%♀ (M25689) in both studies compared to control values at the end of 6 months. These lower values (9.7% and 8.8%) continued to the end of the recovery period. No treatment-related changes in food consumption were observed.

Hematology:

A statistically significant decrease of <10% in the erythrocyte, hemoglobin and packed cell volume were observed at the LD group. Slight decreases in leucocyte and platelet counts (>23% >30%) were seen in all treated groups, most notably in the LD group with regard to leucopenia. Mean platelet counts were increased for both males and females at HD group. Hematologic changes reversed during the recovery period.

Clinical Chemistry:

Drug related changes include a slight increases @10% in mean BUN and slight decreases @12% in total protein in the LD group.

Ophthalmic Observations:

No significant differences between treated and control mice were observed.

Gross Pathology:

Moderate increases in spleen weights were observed doses ≥ 0.5 mg/kg/day (62%) and decreases in ovary and uterine weights about 14-31% were also seen in the LD mice. Decreases of 73% (LD), 70% (MD), and 58% (HD) in testicular weights were observed in the gemcitabine-treated animals. Testes and splenic weights in LD mice remain depressed at the end of recovery period. Splenic weights were reversed in males but not in female mice.

Histopathology:

The LD mice had enlarged spleens due to splenic erythropoiesis. Approximately half of the mice in this group had lymph nodes with lymphoid hypoplasia and chronic histiocytosis on day 183. Lymph node changes were reversible and the splenic size decreased during the recovery phase, except splenic weights remained in females in the LD group. Female sex organs (ovary and uterus) were decreased for the LD groups and these changes were reversible. A decrease in testes weights and severe hypospermatogenesis was present in all treated groups, and these testicular changes were only partially reversible.

**F. A Chronic toxicity study of Gemcitabine HCl given intraperitoneally to CD-1 mice for 6 months with a 6-week reversibility study, Study No. M06591:
(vol. 1.21)**

Dose levels and dose schedules for this study were based on the results from a 6-month study in which a daily dose of 0.5 mg/kg gemcitabine HCl was markedly more toxic than an interrupted dose schedule with much larger weekly doses. The minimal toxic dose in this 6 month study was determined to be 40 mg/kg (120 mg/m²) given weekly for 6 months (the same dose level established in the 3-month study).

CD-1 mice (15/sex/group, 5-6 weeks old) received daily i.p. doses of LY188011 HCl (Lot#G76-9W-2-073 (CT 00132) at 0 (PBS), 0.006 (0.018), 0.06 (0.18) or 0.3 mg/kg (0.9 mg/m²) for 6 months. Ten mice/sex/group were necropsied at the end of 6 months treatment period. Five/sex/group were maintained without gemcitabine for 6 weeks for reversibility study and were terminated at the end of the recovery period. Lot G76-9W2-073 (CT 00132) was used.

Measurements and Observations:

Daily: survival and clinical signs
Weekly: body weight, hematology, clinical chemistry
Termination: gross/histopathology

Results:

Mortality/Clinical signs:

No mortality and no treatment-related clinical signs were observed,

Body weight/Food consumption:

No treatment-related effects on body weight were observed in the females given LD and MD or males given HD gemcitabine. A slight decrease in mean body weight gain (@28%) was observed in HD females during the 3rd through 6th months of treatment and persisted in about half the mice during the reversibility period. No treatment-related changes in food consumption were observed.

Hematology:

HD gemcitabine caused minimal and reversible changes in erythrocytic parameters: decrease in mean total RBC counts (11%) and increase in mean MCV (6%) in males and decreases in mean total RBC (11%) and mean PCV (6%) and increase in mean MCH (6%) in females on 182-183 days.

Clinical Chemistry:

Drug related changes included slight increase in mean serum sodium (@ <10%) and chloride concentrations (<10%) in the HD males. In contrast, these values were decreased in the HD females.

Urinalysis:

No treatment related changes were observed.

Gross Pathology:

On day 183, mean absolute and relative testis weights in males given HD gemcitabine for 6 months were decreased about 70%. After 6 weeks of recovery (or day 224), testis weights were still decreased about 45%. Mean absolute and relative spleen weights in HD males after 6 months treatment increased about 200%. Absolute and relative spleen weights in the other male gemcitabine treatment groups were increased about 30%. Absolute and relative spleen weights were increased about 70% in all gemcitabine-treated female mice. After 6 weeks of recovery, HD males and females still had slightly increased spleen weights (about 30%). On day 183, mean absolute uterine weights in MD females were increased about 42%. These increases were not observed on day 224. Changes in uterine weights were associated with various stages of estrus cycle not related to gemcitabine.

Histopathology:

All males given HD gemcitabine had slight to moderate hypospermatogenesis with decreased numbers of spermatocyte within seminiferous tubules on day 183. After 6 weeks recovery, 3/5 mice had the same effects and the other mice had minimal hypospermatogenesis with a increase in number of mature spermatids. MD and LD gemcitabine treated mice and controls had a very low incidence of hypospermatogenesis. After 6 week reversibility period, hypospermatogenesis was still evident in the HD group but was less prominent, indicating some recovery had occurred. Minimal multifocal inflammation of the liver was observed in all gemcitabine treated mice [males (4/10, 5/10, 4/10) and females (1/10, 2/10, 5/10) in LD, MD and HD, respectively] on day 183. A slight to moderate chronic multifocal mesenteric inflammation was observed in 1/10♂ LD, 1/10♀ MD and 1/10♀ HD gemcitabine treated groups on day 183. Only two MD mice had minimal subacute multifocal inflammation of mesentery on day 224. One male given HD gemcitabine had increased splenic extramedullary hematopoiesis on day 183. No extramedullary hematopoiesis was observed on day 224.

G. **A Chronic toxicity study of Gemcitabine HCl given intravenously to beagle dogs for 6 months with a 6-week reversibility study, Study No. D00191: (vol.1.24)**

Beagle dogs (6 months old) received daily of weekly i.v. bolus Gemcitabine _____ injections for 6 months (see the table below). Controls received phosphate buffered saline. Groups 03 and 04 treated daily and weekly for 6 months followed by a 6 weeks for recovery of treatment-related changes.

Group	# of Animals	Gemcitabine mg/kg(mg/m ²)	Frequency
00*	6M + 6F	0 (0)	daily
01	3M + 3F	0.004 (0.08)	daily
02	3M + 3F	0.04 (0.8)	daily
03	6M + 6F	0.2 (4)	daily
04	6M + 6F	3 (60)	weekly

Measurements and Observations:

Daily:	survival and clinical signs
Weekly:	body weight, hematology, clinical chemistry
Pre-, preterminal:	ophthalmic examination
Pre-, preterminal:	ECG examination
Termination:	gross/histopathology

Results:

Mortality/Clinical signs:

No treatment-related mortality or clinical signs were observed. However, abnormal stools (soft, runny, mucoid) and emesis were seen in some dogs from control and treatment groups during the initial 3 months of the study. Emesis occurred three times in one dog#261214 given 0.04 mg/kg/day on days 2-7 post dose.

Body weight/food consumption:

No statistically significant differences in body weight or food consumption occurred during treatment or recovery phase.

Ophthalmic examination:

No treatment-related ophthalmic changes were observed at 6 months or at the end of the recovery phase.

Hematology:

Dogs given 0.2 mg/kg/day (mkd) or 3 mg/kg/week (mkw) showed significant decreases in erythrocytes and lymphocytic parameters during the treatment which were reversed during the recovery phase. In HD group, minimal decreases in total erythrocyte counts (@15-25%) and increases in MCV (@14% ♂; 15% ♀) and MCH (@16% ♂; 18% ♀) on days 29 and 59. Males and females treated with 0.2 mkd or 3 mkw had decreased leukocyte (-24% to -45% ♂; -30% to -46% ♀), lymphocyte (-21% to -49% ♂; -32% to -39% ♀) and neutrophil counts (-46% to -58% ♂; -32% to -59% ♀) from days 17 through termination of the reversibility phase. Bone marrow samples were morphologically unremarkable.

Clinical Chemistry:

Drug related changes included slight increases in AST (32% ♂, 29% ♀) and triglycerides (57% ♂, 45% ♀) in dogs given 3 mkw and decreases in BUN (-25% ♂, -34% ♀) in dogs given 0.2 mkd and creatinine (-25% ♂/♀) values in 0.2 mkd and in 3 mkw groups.

Urinalysis:

No treatment-related changes were seen during the treatment or recovery phase.

ECG:

No treatment-related ECG changes were reported. However, one dog (#244823) given 0.2 mkd group had one missing ventricular complex following a P wave. This finding is occasionally seen in normal beagle dogs and was not considered to be drug-related.

Mean heart rate was significantly decreased compared to controls on day 183 in one male dog (0.2 mkd group) at 1 hour post treatment. The differences were slight in magnitude (30 beats/min) and were not considered to be of toxicologic significance.

Gross or Histopathology:

No drug-induced gross or histopathologic findings were observed during the 6-month treatment period or the 6-week reversibility period.

Summary of Toxicology:

Acute toxicity studies were conducted to compare gemcitabine and its _____ and major degradation product in mice and rats. In mice, gemcitabine and its _____ were given at single i.v. dose of 500 mg/kg, no differences were noted in acute toxicity of _____ as compared to the parent compound. In rats, toxicity of the pyranose impurity of gemcitabine (given 90-500 mg/kg, intraperitoneally) and dFdU, the major degradation product/ _____ (given 45-330 mg/kg intravenously) was similar to or less than that of the parent compound. In acute dog study, i.v. doses of gemcitabine (3, 12 mg/kg, day 1; 18, 24 mg/kg, day 15) produced mild g.i. toxicity (soft stools), mild increase in AST values and neutropenia (reversible).

Chronic toxicity studies of gemcitabine were determined in 6-month studies in mice by the intraperitoneal route and in a 6-month study in dogs by the intravenous using daily, biweekly and weekly doses as in the following table.

Chronic toxicity studies can be summarized:

Species	Duration	Route	Daily	Dose (mg/kg)		Weekly
				Biweekly	Weekly	
Mouse	6 month ^a	IP	0.5	5	40	
Mouse	6 month ^b	IP	0.006 0.06 0.3	-	-	
Dog	6 month ^b	IV	0.004 0.04 0.2	-	3	

a-2-month reversibility period

b-6 week reversibility period

Gemcitabine administered to mice on a daily dose of 0.5 mg/kg resulted in marked toxicity whereas much larger total weekly dose levels were well tolerated. The major toxicity included decreased body weight, decreased erythrocyte and lymphocyte parameters, increased BUN, increased splenic erythropoiesis, lymphoid hypoplasia, histiocytosis of the lymph nodes, and hypospermatogenesis of testes. All these changes were partially or totally reversed at the end of 2 months recovery period. The minimal toxic dose of 40 mg/kg/week (120 mg/m²/week) was the same for both the 3-month and 6 month studies.

In the second 6-month study in mice, no gemcitabine-related deaths were observed. Body weights were slightly decreased in mice given 0.3 mg/kg after the third month of the study. No treatment-related clinical signs of toxicity, food consumption, leucocytes and thrombocytes, clinical chemistry, or urinalysis were observed. Minimal hematologic changes (↓RBC, PCV) were seen in mice given 0.3 mg/kg (erythrocyte effects were resolved during the 6 week recovery period). Increased spleen weights in mice given 0.3 mg/kg were partially reversed during recovery. Decreased testes weights accompanied by hypospermatogenesis were seen in males given 0.3 mg/kg daily dose. Hypospermatogenesis occurred in the 0.3 mg/kg but not in the 0.006 mg/kg. These effects were partially reversed after discontinuation of treatment. Gemcitabine HCl administration to mice on a daily schedule was well tolerated. The signs of toxicity produced in this study were similar to those seen in previous 3- and 6-month studies. The minimal toxic dose was 0.06 mg/kg/day (or 0.18 mg/m²/day).

In the chronic 6-month toxicity study, all dogs survived. No treatment-related clinical signs of toxicity, ophthalmic changes, ECG changes, or effects on the body weights were observed. Erythrocyte counts were decreased in dogs given 0.2 mg/kg/day. A slight decreases in lymphocyte and neutrophil counts were seen in the 0.2 mg/kg/day and 3 mg/kg/week. These effects were reversed. No treatment-related organ weights or pathologic findings were reported. The minimal toxic dose of 3 mg/kg/week (60 mg/m²/week) was the same for both the 3-month and 6-month studies. Additionally, the daily minimal toxic dose was determined to be 0.04 mg/kg (0.8 mg/m²) in dogs.

IV. Special Toxicity Studies:

Evaluation of the Immunogenicity of LY188011 HCl in male guinea pigs, Study No. G02588 and G02888

In Vitro Hemolysis and Serum Flocculation tests using Gemcitabine HCl in pooled whole blood and serum beagle dogs and rhesus monkeys, Study No. D05189 and P04889

Acute Dermal Irritation study of Gemcitabine in NZW rabbits, study No. B01492

Evaluation of the Immunogenicity of LY188011 HCl in male guinea pigs, Study No. G02588 and G02888: (vol. 1.25)

Guinea pigs(5/group, 4-7 weeks old) were sensitized with LY188011 in aluminum hydroxide gel(sc) or in PBS(ip) for 30+ days. Four groups received by subcutaneously 5 doses of either LY188011 at 0.2 or 2.0 mg/kg/week, LY188011/OVA at 2.0 mg LY188011/kg/week plus 0.4 mg ovalbumin/kg/week, or ovalbumin alone at 0.4 mg/kg/week. In addition, two groups received i.p. injections of LY188011 at 0.2 or 2.0 mg/kg twice weekly for a total of 9 injections. A control group was untreated. Animals were challenged on day 42 intravenously with 1.0 ml/kg antigen and observed for signs of acute anaphylaxis (AA).

In passive cutaneous anaphylaxis, a group of guinea pigs were injected intradermally with sera (1:10 and 1:100 dilution in PBS) from guinea pigs 4 days before the AA (acute anaphylaxis) challenge. At 24 hrs later, animals were challenged i.v. with 2.0 ml/kg antigen in Evans blue dye. Passive cutaneous anaphylaxis (PCA) was measured by the size of the blue spot near the injection site.

No significant changes in body weight were seen with LY188011. In the challenge group, neither LY188011 or LY188011 conjugated with keyhole limpet hemocyanin showed anaphylactic symptoms in any guinea pig challenged with LY188011 or LY188011/OVA. Animals with LY188011 conjugated with ovalbumin challenged to ovalbumin produced AA death in 5/5 animals. In the PCA group, sera from LY188011/OVA did not induce PCA responses with LY188011, LY188011/KLH or dialyzed LY188011/KLH, positive responses were seen when challenge to ovalbumin. Ovalbumin produced a 252 mm² at a 1:200 dilution and 199 mm² at a 1:1000 dilution LY188011/OVA conjugate sera.

LY188011 did not induce immune responses in guinea pigs in assays for acute anaphylaxis and passive cutaneous anaphylaxis.

In Vitro Hemolysis and Serum Flocculation tests using Gemcitabine HCl in pooled whole blood and serum beagle dogs and rhesus monkeys, Study No. D05189 and P04889: (vol. 1.25)

Gemcitabine (LY188011 HCl) was tested for its potential to cause in vitro hemolysis and protein flocculation.

In hemolysis, 3 venous blood samples collected from normal dogs and monkeys were pooled for each species. Equal volumes (200 ul) of distilled water, 0.9% saline solution, and gemcitabine (7.5 mg/ml) were added to the 100% standard, 0% standard, and test sample, respectively. The tubes were mixed gently and incubated at room temp for 1 hr. After incubation, hemolytic activity was determined using a spectrophotometer. The 100% standard was considered to have complete (100%) hemolysis. Hemolysis of 0% standard and the test solution was compared.

In flocculation, 3 venous samples obtained from dogs and monkeys were centrifuged and the serum from each species were pooled. Volumes of 0, 0.01, 0.025, 0.10 and 0.25 ml of solution containing 7.5 mg/ml gemcitabine was added to 0.5 ml of the pooled serum from each species. The tubes were examined for flocculation following incubation of 30-60 minutes at room temp and 37°C.

In vitro hemolysis was not observed in solution containing 7.5 mg/ml gemcitabine in dog or monkey whole blood. Serum flocculation was not observed in solution containing 7.5 mg/ml gemcitabine in dog or monkey serum.

Acute Dermal Irritation study of Gemcitabine in NZW rabbits, study No. B01492: (vol. 1.25)

Three female NZW rabbits were shaved focally on the back and a moistened pad containing gemcitabine at a concentration of 1 g/kg was wrapped over the shaved area for approximately 24 hrs.

Results:

Four days after gemcitabine exposure, one rabbit developed a red-colored nasal discharge, shallow breathing, and was lethargic; one had a nasal discharge, shallow breathing and was lethargic; the third rabbit was hypoactive. The two rabbits with nasal discharge died about 24 hrs later. No lesions appeared on the skin indicating gemcitabine was not a dermal irritant. However, both rabbits had wetness around the nose and mouth. Both rabbits had multiple variably sized hemorrhages in the lungs and multifocal hemorrhages in the cecum. Other portions of the intestinal tract were filled with

gas and fluid contents. Thymus of one rabbit was edematous while others had petechial hemorrhages. The third rabbit survived, but remained hypoactive. Gross pathology findings are consistent with those observed for the delayed toxicity in rats exposed to a single large i.v. dose of gemcitabine.

The median lethal dose of gemcitabine given i.v. doses to rats is @1400 mg/m². Absorption of only 10% of the exposure dose in the present study would be sufficient to exceed that figure (1100 mg/m² in rabbit).

Shaving and moistening of the skin promoted drug absorption. Dermal absorption which resulted in systemic toxicity of gemcitabine has not been described previously. No imminent hazard is posed by dermal absorption. However, information about possible dermal absorption should be included in precautions for handling of gemcitabine while in solution.

Summary of Special Toxicity Studies:

The potential immunogenicity of LY188011 HCl was tested in Hartley albino guinea pigs. In acute anaphylaxis, guinea pigs were sensitized with LY188011 at 0.2 or 2.0 mg/kg/week with or without ovalbumin in aluminum hydroxide gel(sc) or in PBS(ip) for 30+ days. LY188011 HCl, alone or when combined with ovalbumin, did not induce immune responses in guinea pigs in assays for acute anaphylaxis and passive cutaneous anaphylaxis.

Gemcitabine did not induce hemolysis or serum flocculation using dog or monkey whole blood or serum in vitro.

An acute dermal irritation of gemcitabine was evaluated in 3 rabbits with a moistened pad containing gemcitabine at a concentration of 1 g/kg. After 4 days gemcitabine exposure, 2/3 rabbits exhibited drug-related systemic toxicities (deaths, hypoactivity, nasal discharge, shallow breathing) and drug-induced lesions were consistent with those observed in the toxicity studies in rats exposed to a single large dose of gemcitabine. No dermal irritation was seen.

V. REPRODUCTIVE TOXICOLOGY:

A. 3-Month Male Fertility Study of Gemcitabine HCl given intraperitoneal injections to B6C3F1 mice. Study #M00689: (vol 1.25)

Male mice (20/group, @ 5 weeks old) were given 7 daily i.p. doses of 0, 0.05, or 0.5 mg/kg LY188011 (Lot-FF8L80A0) or weekly doses of 3.5 or 10 mg/kg/week (mkw) for 10 weeks prior to mating, during mating, and up to 13 weeks postmating. Males were cohabitated with untreated females for 2 weeks. Effects of LY188011 on the male fertility were assessed.

Measurement and Observation:

Daily: mortality, clinical observations

Weekly: body weight

Daily during copulation: presence of expelled/retained copulatory plugs and vaginal lavage.

At termination: necropsy of females (day 17-18 of pregnancy)-implantations, early/late resorptions, live/dead fetuses, fetal malformations.

Necropsy of males (day 18) gross and histological examination of testes.

Results:

Mortality/Clinical Observations:

Five males at 0.05, 2 males at 0.5 mkd, and 4 males in the control group died. Reasons for the deaths were not given. No treatment related clinical signs or body weights were observed. Occasional alopecia was seen in the treated males and untreated females. Overall body weight gains of females at 0.5 mkd were slightly decreased @ < 10% during the latter part of gestation. This may be due to the lower number of fetuses in this group.

Gross/Histopathology:

Testicular weight was reduced @30% in 3.5 mkw and 60% in 10 mkw groups. Greatest reduction in testicular weight (@68%) was in the 0.5 mkd group. Decreases in testes weight correlated directly with the severity of hypospermatogenesis. Gemcitabine administered to male mice on a daily dose of 0.5 mg/kg (a total dose of 35 mg/kg/10 weeks) resulted in moderate to severe hypospermatogenesis whereas much larger total weekly dose (100 mg/kg/10 weeks) resulted in minimal to moderate hypospermatogenesis. A slight to minimal hypospermatogenesis occurred at 3.5 mkw. Since this drug is an antimetabolite, more frequent exposure even at 2.8-fold lower dose resulted in a more permanent effect on rapidly dividing germ cells.

Mating Performance and Fertility:

All surviving males mated. There were 100%(18/18), 89% (16/18), 47%(9/19), 100%(20/20) and 85%(17/20) pregnancies at given daily doses of 0, 0.05, 0.5 mg/kg, weekly doses of 3.5 or 10 mg/kg, respectively. Only the 0.5 mkd group had significantly fewer pregnancies than in the controls. The total number of implantations were significantly reduced in the 0.5 mkd group. There were no effects on the resorptions, live/dead fetuses, and fetal morphology.

B. A Segment I Female Fertility Study of Gemcitabine HCl given intravenous injections to CD-1 mice, Study No. M04190: (vol. 1.27)

Female mice (CD-1, 25/group, @9 wks) were given Gemcitabine (Lot CT-8975-9C) daily i.v. doses of 0, 0.05, 0.25 or 1.5 mg/kg/day for 2 weeks premating and through gestation (days 6-18).

Females were mated with untreated males for 2 weeks.

Measurement and Observations:

Daily: mortality, clinical observation

Weekly: body weight

Daily during copulation: presence of copulatory plug and vaginal lavage.

At Termination: necropsy of females (day 18 gestation)-implantation, resorptions, live/dead fetuses, fetal morphology

Results:

Mortality/Clinical Observations:

One female each at HD and LD, and 2 females in the control group died immediately after dosing. These deaths were not drug-related. No other clinical signs were observed during the study.

Body weight/Food consumption:

Body weights were depressed at 1.5 mkd group on gestation days 14 and 18 ($p \leq .05$). Overall body weight gain at 1.5 mkd was decreased @38% during the latter part of gestation (days 14-18) and total body weight gain of the same group was significantly decreased by @42%. In the original submission, food consumption was depressed @25% in the HD group during gestation days (14-17). In an Amendment dated 10/2/95, sponsor reported that food consumption was depressed <10% during pre-mating days 8 through 14 in the HD group.

Hematology:

In the HD group, a slight increase was seen for erythrocytes (<10%), Hb (@10%) and packed cell volume (<10%) for 21 days. Mean corpuscular volume (<10%) and mean corpuscular hemoglobin (<10%) were slightly increased. At termination, there were no significant differences in erythrocyte, thrombocyte, leukocyte counts or mean corpuscular hemoglobin

Gross/Histopathology:

No significant differences were observed in absolute or relative weights of maternal kidneys, heart, and brain, but the absolute and relative ovary weights (29%, 28%, LD; 24%, 21%, MD) were increased at a statistically significant level. Liver (-18%) and uterine weights (-78%) were decreased and thymus (23%) and spleen weights (45%) were increased in HD females. No gross lesions were observed and no histological examinations were performed.

Mating Performance and Fertility:

No treatment related effects were seen on pre-coital periods, mating performance or fertility. There were 18, 21, 23 and 20 pregnancies from the 0, 0.05, 0.25 and 1.5 mg/kg/day groups, respectively.

Maternal Reproduction Parameters:

Maternal reproductive parameters from female mice given i.v. doses of LY188011

Parameters	Treatment Group			
	0	1	2	3
Implantation				
Number	mean 11.2	10.2	11.3	12.2
Live fetus/litter				
Number	mean 10.4	9.6	10.1	2.1
%	93.22	94.19	89.53	16.81
Early resorption/litter				
Number	mean 0.8	0.6	1.1	10.1
%	6.78	5.81	10.47	82.74
Total resorption/litter				
Number	mean 0.8	0.6	1.1	10.1
%	6.78	5.81	10.47	83.19
Litters with non-live implants				
Number	mean 9	8	16	17
%	50.0	40.0	72.7	100.0
Litters with total resorptions				
Number	mean 0	0	0	9
%	0	0	0	52.9

Groups: 0= control, 1= 0.05 mg/kg/day; 2= 0.25 mg/kg/day; 3= 1.5 mg/kg/day

Females 2075 and 3061 (MD and HD group) delivered early on gestation day 18 and were excluded. Females 1066 and 3063 (LD and HD group) were excluded because of the implantation sites observed during uterine evaluation. And female 3052 (HD) was excluded because of the loss of part of the external fetal evaluation data. The number of implantations were not affected by gemcitabine treatment. The percent of live fetuses/litter decreased in the HD group because of an increase in the percent of early resorptions/litter, the percent of litters with resorptions, litters with nonlive implants, and litters with total resorptions were increased. No dead fetuses were seen, but 9 females at HD had litters that were completely resorbed.

Fetal Parameters:

The numbers of fetuses available for examination include 188, 191, 231, and 37 from the 0, 0.05, 0.25 and 1.5 mg/kg/day groups, respectively. Fetal weight was depressed @25% (♂/♀) and an increase @26% in fetal runts occurred in the HD group. At HD, the percent of fetuses with deviations/litter was higher. A higher incidence of incomplete ossification of various skeletal structures (proximal and distal phalanges; metatarsal bones; frontal, interparietal, occipital, and parietal skull bones; sternebra) occurred at the HD group. Three fetuses each MD and LD groups had incomplete ossification of forepaw-proximal phalanges. Incomplete ossification of forepaw-digital phalanges was observed in all treated and control group. Three fetuses in the HD group had kidney cavitation (visceral malformation). The percent of affected implants/litter was elevated in the HD due to the increase in the early resorptions/litter. Four fetuses in the LD group had fused rib cage-sternebra.

TABLE 12 (CONTINUED) DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE MICE GIVEN INTRAVENOUS DOSES OF 188011 HYDROCHLORIDE. STUDY M04190

DEVIATIONS	TREATMENT GROUP			
	00	01	02	03

CONCEPTUSES (LITTERS) AFFECTED				

EXTERNAL				
EXTREMITY-BENDING-FLEXION	0 (0)	1 (1)	1 (1)	0 (0)
HEAD/NECK-CRANIUM-HEMATOMA	0 (0)	0 (0)	0 (0)	1 (1)
HEAD/NECK-HEMATOMA	0 (0)	0 (0)	0 (0)	1 (1)
VISCERAL				
URINARY SYSTEM-KIDNEY-CAVITATION	0 (0)	0 (0)	0 (0)	3 (3)
OSSELETAL				
APPENDAGES-FOREPAW-DISTAL PHALANX	9 (5)	13 (8)	24 (9)	12 (5)
-INCOMPLETE OSSIFICATION				
APPENDAGES-FOREPAW-METACARPAL	0 (0)	0 (0)	0 (0)	1 (1)
-INCOMPLETE OSSIFICATION				
APPENDAGES-FOREPAW-PROXIMAL PHALANX	0 (0)	3 (3)	3 (2)	10 (6)
-INCOMPLETE OSSIFICATION				
APPENDAGES-HINDPAW-DISTAL PHALANX	0 (0)	1 (1)	0 (0)	5 (5)
-INCOMPLETE OSSIFICATION				
APPENDAGES-HINDPAW-METATARSAL	0 (0)	0 (0)	0 (0)	2 (2)
-INCOMPLETE OSSIFICATION				
APPENDAGES-HINDPAW-PROXIMAL PHALANX	0 (0)	1 (1)	0 (0)	7 (6)
-INCOMPLETE OSSIFICATION				
AXIAL SKELETON-RIB CAGE-RIB-NAVY	0 (0)	0 (0)	1 (1)	0 (0)
AXIAL SKELETON-RIB CAGE-STERNEBRA-SEPTATE	1 (1)	2 (2)	2 (2)	1 (1)
AXIAL SKELETON-RIB CAGE-STERNEBRA-EXTRA	1 (1)	1 (1)	1 (1)	0 (0)
AXIAL SKELETON-RIB CAGE-STERNEBRA-FUSED	0 (0)	1 (1)	0 (0)	0 (0)

C. A developmental toxicology study of Gemcitabine HCl given intravenously to female CD-1 mice, Study No. M03090: (vol. 1.28)

This study was performed to evaluate teratogenic and postnatal effects of gemcitabine in pregnant CD-1 mice.

A. Teratology Study:

Pregnant female CD-1 mice (25/group) were given i.v. doses of 0, 0.05, 0.25 or 1.5 mg/kg/day (0, 0.015, 0.75, or 4.5 mg/m²/day) on gestation days 6 through 15. On gestation day 18, females were euthanized and uterine contents were examined for fetal viability, weight, and morphology.

Measurement and Observations:

Daily: Mortality, signs of toxicity
 Weekly: body weight, food consumption, hematology
 Termination: necropsy of females(day 18 gestation) live/dead fetuses, size, fetal malformations.

Results:**Mortality/Clinical Observations:**

No treatment related maternal mortality occurred. Slight increases in the incidence of vaginal discharge and abortion were observed in the HD group. Significant decreases in body weight (@33%), and the overall body weight gains (@40%) were observed in the HD group during the gestation in both teratology and postnatal study. This may be related to the decreased number of animals maintaining pregnancy and decreased litter size.

Maternal Gross Observations:

Females that were killed on gestation day 18, showed a dose-related increase in spleen weights [LD (@20%), MD (@40%) and HD (@98%)], but these effects were not observed in females killed after weaning their pups. Thymus weights were increased (@38%) but the liver weight was decreased (@-14%) in the HD group.

Reproductive Parameters:

The overall fertility index was 93% and did not vary significantly across the experimental groups. The numbers of pregnant females for cesarean section on gestation day 18 were 20, 23, 20, and 19 from the 0, 0.05, 0.25, and 1.5 mkd treatment groups. Three females aborted between gestation days 12 and 16 in the HD group. The mean number of implantations were similar in all groups. An increase in the percentage (@64%) of early resorption in the HD group resulted in fewer live fetuses (@34% vs @94% control) and increased total resorption (@66%) and nonlive implants (@66%).

Maternal reproductive parameters from female mice given i.v. doses of LY188011

Parameters	Treatment Group			
	0	1	2	3
Implantation				
Number	mean 11.9	11.1	11.5	10.8
Live fetuses/litter				
Number	mean 11.1	10.1	10.5	4.1
%	93.7	90.1	89.2	34.2
Early resorption/litter				
Number	mean 0.8	1.0	1.1	6.5
%	6.27	9.63	10.78	64.15
Total resorption/litter				
Number	mean 0.8	1.1	1.1	6.7
%	6.27	9.94	10.78	65.78
Non-live implants/Litter				
Number	mean 0.8	1.1	1.1	6.7
%	6.27	9.94	10.78	65.78
Litters with non-live implants				
Number	mean 11	14	14	18
%	0	0	0	42.1

Groups: 0= control; 1= 0.05 mg/kg/day; 2= 0.25 mg/kg/day; 3= 1.5 mg/kg/day

Fetal Parameters:

Mean body weights of male (@66%) and female (@33%) fetuses were significantly reduced in the HD group. About one-half of the malformed fetuses in the HD group were classified as runts.

Malformations were increased in male and female fetuses from the HD group but increase was not significant for females. Malformations included cleft palate, digital malformations, protruding brain, open eyelids, visceral, and skeletal malformations (lateral curvature of the sternum). Affected implants/litter totaled 8.1%, 12.9%, 11.6%, and 70.3% for the control, LD, MD, and HD treatment groups, respectively (see the following tables).

Fetal parameters from female mice given i.v. doses of LY188011 HCl

Parameters	Treatment Groups			
	0	1	2	3
Affected implants/litter				
Mean	1.0	1.3	1.2	7.3
%	8.10	12.89	11.59	70.30
Litters with affected implants				
Mean	14	17	14	18
%	70.0	73.9	70.0	94.7
Litters with live fetuses				
Males				
Mean	5.3	4.5	5.5	4.3
%	45.57	45.04	53.45	66.51
Females				
Mean	5.8	5.6	5.0	2.8
%	54.43	54.97	46.56	33.49
Fetal weight/litter (♂ + ♀)				
Mean	1.33	1.37	1.33	1.03
Fetal runs/litter				
Mean	0.6	0.0	0.0	1.5
%	5.0	0.34	0.0	19.86
Normal fetuses/litter				
Mean	7.6	7.0	7.3	4.1
%	67.91	69.86	68.51	29.30
Fetuses with malformations/litter				
Mean	0.1	0.3	0.1	1.9
%	1.83	3.08	0.89	19.46
Litters with fetuses having malformations				
Mean	3	6	2	5
%	15.0	26.1	10.0	45.5
Fetuses with malformations/litter				
Male				
Mean	0.1	0.1	0.1	0.8
%	0.66	2.53	0.72	23.10
Female				
Mean	0.1	0.2	0.1	0.3
%	1.50	2.60	1.32	5.00

Groups: 0= control; 1= 0.05 mg/kg/day; 2= 0.25 mg/kg/day; 3= 1.5 mg/kg/day

TABLE 16 (CONTINUED) DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE MICE GIVEN INTRAVENOUS DOSES OF 188011 HYDROCHLORIDE, STUDY NO1090

MALFORMATIONS	TREATMENT GROUP			
	00	01	02	03

CONCEPTUSES (LITTERS) AFFECTED				

EXTERNAL				
ABDOMEN-BODY WALL-VISCERAL ORGANS-PROTRUDING	1 (1)	0 (0)	0 (0)	0 (0)
EXTREMITY-HINDLIMB-PAW-DIGIT-EXTRA	0 (0)	0 (0)	0 (0)	2 (2)
EXTREMITY-HINDLIMB-PAW-DIGIT-SHORT	0 (0)	0 (0)	0 (0)	1 (1)
HEAD/NECK-CRANIUM-BRAIN-PROTRUDING	1 (1)	1 (1)	0 (0)	1 (1)
HEAD/NECK-HARD PALATE-CLEFT	1 (1)	2 (2)	0 (0)	0 (0)
HEAD/NECK-JAW-SMALL	0 (0)	0 (0)	1 (1)	4 (3)A
HEAD/NECK-EYELID-OPEN	1 (1)	2 (2)	0 (0)	0 (0)
VISCERAL				
CARDIOVASCULAR SYS-HEART-ENLARGED	1 (1)	0 (0)	0 (0)	0 (0)
DIGESTIVE SYSTEM-SOFT PALATE-CLEFT	0 (0)	0 (0)	0 (0)	3 (3)A
RESPIRATORY SYSTEM-LONG-POSTCAVAL LOBE-SMALL	0 (0)	0 (0)	1 (1)	1 (1)
URINARY SYSTEM-BLADDER-ENLARGED	1 (1)	0 (0)	0 (0)	0 (0)
URINARY SYSTEM-KIDNEY-SMALL	0 (0)	1 (1)	0 (0)	0 (0)
SKELETAL				
APPENDAGES-FOREPAW-PROXIMAL PHALANX-SPLIT	0 (0)	1 (1)	0 (0)	0 (0)
APPENDAGES-HINDPAW-DISTAL PHALANX-ABSENT	0 (0)	0 (0)	0 (0)	1 (1)
APPENDAGES-HINDPAW-DISTAL PHALANX-EXTRA	0 (0)	0 (0)	0 (0)	1 (1)
APPENDAGES-HINDPAW-METATARSAL-EXTRA	0 (0)	0 (0)	0 (0)	1 (1)
APPENDAGES-HINDPAW-PROXIMAL PHALANX-ABSENT	0 (0)	0 (0)	0 (0)	1 (1)
AXIAL SKELETON-RIB CAGE-STERNUM	0 (0)	0 (0)	0 (0)	1 (1)
-LATERAL CURVATURE	0 (0)	0 (0)	0 (0)	1 (1)
SKULL-CALVARIA-INTERPARIETAL BONE-ABSENT	0 (0)	1 (1)	0 (0)	0 (0)
SKULL-CALVARIA-OCCIPITAL BONE-SMALL	0 (0)	1 (1)	0 (0)	0 (0)
SKULL-CALVARIA-PARIETAL BONE-ABSENT	0 (0)	1 (1)	0 (0)	0 (0)

An increase in the incidence of cleft palate contributed to the significant increase in

malformations in the HD group. Isolated cases of skeletal malformations were noted in the HD and LD group.

B. Postnatal Study:

Gemcitabine treated pregnant females (20/group) were allowed to deliver and f_1 offspring development, including physical and behavioral assessment, was monitored until weaning. After weaning, maternal animals were killed and examined and selected organs were weighed. Gross examinations (internal, external) were performed on postpartum day 21 of those f_1 offspring not selected to continue on study. F_1 generation is randomly selected f_1 offspring on postpartum day 1 to continue on study for behavioral and reproductive assessment. The F_1 females were allowed to deliver and maintain their f_2 progeny through postpartum day 1.

Measurement and Observations:

Daily: Mortality, signs of toxicity
 Weekly: body weight
 Days 30-60: behavioral assessments (pre-, postweaning)
 13 weeks: mating, reproductive assessments
 Termination: necropsy of F_0 females and f_1 offspring on postpartum Postnatal Study:

In the postnatal study, the overall fertility index was 99% and did not vary significantly across experimental groups. One female in the LD aborted on gestation day 14. The numbers of animals for cesarean sections were 19, 19, 19, and 10 for the control, LD, MD, and HD treatment groups, delivered litters. Gestation length was slightly increased (18.8 day) in the HD treatment group when compared to the controls (18.2 day). The liveborn index was comparable (96-99%) in all groups. In the high dose group, reduced liveborn litter size (@27%) was observed.

TABLE 18 SUMMARY OF REPRODUCTION PARAMETERS FOR FEMALE MICE GIVEN GEMCITABINE HCL INTRAVENOUSLY. TERATOLOGY STUDY M03090, F_0 POSTNATAL SEGMENT.

	Treatment Group (mg/kg/day)			
	0	0.05	0.25	1.5
Total Females	20	20	20	20
Total Pregnant	19	20	20	20
Fertility Index (%)	95	100	100	100
Deaths	0	0	1	0
Aborted: Killed	0	1	0	0
Pregnant: No delivery	0	0	0	10
Females with Litters	19	19	19	10
Gestation Length ^a (Mean Days \pm SE)	18.2 \pm 0.1	18.4 \pm 0.2	18.4 \pm 0.1	18.8 \pm 0.2*
Liveborn Index ^b (Mean % \pm SE)	96.4 \pm 2.1	93.8 \pm 5.3	98.9 \pm 0.7	99.0 \pm 1.0
Liveborn Litter Size ^c (Mean \pm SE)	10.3 \pm 0.5	9.8 \pm 1.0	10.5 \pm 0.5	7.5 \pm 1.3
Live Litter Size ^d (Mean \pm SE)	10.6 \pm 0.5	11.5 \pm 0.5	10.4 \pm 0.5	7.2 \pm 1.7**

^a ANALYSIS OF VARIANCE, SIGNIFICANT TREATMENT EFFECT, $P \leq .05$.
^{*} STUDENT-NEWMAN-KEULS TEST, $P \leq .05$ VERSUS 0 MG/KG/DAY GROUP.
^{**} STUDENT-NEWMAN-KEULS TEST, $P \leq .01$ VERSUS ALL OTHER TREATMENT GROUPS

^b Proportion of progeny alive on Postpartum Day 0.
^c Number of live progeny observed on Postpartum Day 0.
^d Number of live progeny observed on Postpartum Day 1.

Progeny Observations and Necropsy Findings-F₀ Postnatal Segment:

On postpartum day 0 and 1, dead pups from the 0 (9), 0.05 (5), 0.25(6), and 1.5 mkd(7) groups, respectively, were examined. Minor skeletal anomalies were found in 5, 6 and 2 pups in the 0, 0.25, and 1.5 mkd groups. Malformations include cleft palate (5), digital malformations (1), and protruding brain (1). From postpartum days 2 to 21, 7 pups (1, 3, and 3) in control, LD and MD groups showed minor skeletal anomalies.

TABLE 19 SUMMARY OF OBSERVATIONS FOR PROGENY FROM FEMALE MICE GIVEN GEMCITABINE HCL BY INTRAVENOUS INJECTION. MOUSE TERATOLOGY STUDY M03090. F₀ POSTNATAL SEGMENT.

	Treatment Group							
	00		01		02		03	
	M	F	M	F	M	F	M	F
Pups found dead ^a	3	6	4	2	3	7	2	4
No substantive findings	1	3	4	2	0	1 ^b	1	1
Minor skeletal anomalies	2	3	0	0	3 ^b	3 ^b	1	1
Trauma to paw from tattooing	0	0	0	0	0	1	0	0
Cleft Palate	0	0	0	0	1 ^b	2	0	2 ^b
Protruding Brain	0	0	0	0	0	1	0	0
Digital Malformation	0	0	0	0	0	0	0	1 ^b
Tip of tail missing	0	0	0	1	0	0	0	0
Trauma to paw from tattooing	0	0	0	0	1	0	0	0
Hydronephrosis	0	0	0	0	1	0	0	0
Trauma to paw from tattooing	0	0	0	0	1	0	0	0
Displaced testis	0	0	0	0	0	0	1	0

^aIn addition, 1, 2, 0, and 1 dead progeny in Treatment Group 00 (late resorption), 01, 02, and 03, respectively, were partially cannibalized. Sex could not be determined. Of the specimens examined, no substantive findings were observed.

^bOne pup in common.

Progeny Measurements- F₀ postnatal Segment:

There was a reduction in the number of litters with live-born progeny, total progeny, and progeny survival in the HD treatment group. No treatment-related differences were observed in sex indices, preweaning body weights, pinna detachment on postpartum day 5, hair coat appearance on pp day 10, incisor eruption on pp days 11-13, eye opening on pp day 15-17, testes descend on pp day 21 and 28, or vaginal patency on pp day 35 and 42.

Preweaning Behavioral Assessment:

During preweaning period, no significant differences were observed in negative geotaxic response on postpartum day 5 and 6 of the F₁ animals from the control and gemcitabine treatment groups.

Survival/Signs of toxicity- F₁ Generation:

No animals died during reproductive phase. One control male died during the first week of growth phase. No maternal toxicity was seen with gemcitabine in F₀ generation.

Body weights-F₁ generation:

No significant treatment-related differences in the body weights for the F₁ were observed during the growth phase, the reproductive phase and terminal phase.

Organ Weights- F₁ Generation:

Terminal organ weights were determined after completion of the reproductive phase of the study. In F₁ males, the absolute and relative weights of kidney, liver, heart, spleen, thymus, testes, prostate and brain were similar among all treatment-derived groups. In F₁ females, the absolute and

relative weights of kidney, liver, heart, spleen, thymus, and uterine were similar among all treatment-derived groups. Relative ovary weight (@ 9-11%), and absolute brain weight was decreased (@ -7% 10%) in the HD treatment-derived group.

Postweaning Behavioral Assessments-F₁ Generation:

Males in the LD and HD treatment groups were less reactive than controls in the auditory startle habituation test. There were no adverse findings for the F₁ treatment derived animals in 30-day and 60-day activity levels of inactive or passive avoidance performance.

Mating Performance and Fertility -F₁ Generation:

Mating indices, precoital period, and fertility indices were not affected in the gemcitabine treatment-derived litters.

Reproductive and Progeny Measurements:

Progeny survival, live litter size, litter weight, and sex indices were not affected in the gemcitabine treatment-derived litters.

Pathology -F₀ and F₁ Generation:

No gross pathology findings were observed in the F₀ teratology segment or postnatal segment or in the F₁ generation. One control male from the F₁ generation appeared thin and dehydrated for unclear reasons. No histopathology data was submitted.

D. A Developmental Toxicology study of Gemcitabine HCl given intravenously to NZW Rabbits, Study No. B00291: (vol. 1. 31)

Pregnant rabbits(20/group) were given i.v. doses of 0, 0.0015, 0.005 or 0.1 mg/kg/day (0, 0.0165, 0.055, or 1.1 mg/m²/day) on gestation days 6 through 18. Body weight, food consumption and clinical signs were monitored. Animals were euthanized on gestation day 24 to evaluate fetal viability, weight, and morphology.

Measurements and Observations:

Daily: Mortality, signs of toxicity

Weekly: body weight, food consumption, hematology

Termination: necropsy of females(day 18 gestation) live/dead fetuses, size, fetal malformations.

Results:

Maternal Survival/Body Weight and Food Consumption:

There were no treatment related maternal mortality or clinical signs. Body weight and food consumption were not affected by gemcitabine treatment during gestation.

Hematology:

Slight decreases in erythrocytic parameters (RBC count @12%, Hb <10%, PCV <10%) were observed at the HD but not at the lower doses. Leukocyte and thrombocyte counts were not affected by gemcitabine treatment.

Maternal Reproduction Parameters:

The numbers of corpora lutea and implantations did not vary between treatment groups. Fetal viability and weight were depressed in the HD group due to an increased incidence of early resorption. Fetal viability was not adversely affected by gemcitabine treatment at the MD or LD groups.

Maternal reproductive parameters from female rabbits given i.v. doses of LY188011 HCl

Parameters		Treatment Groups			
		0	1	2	3
Corpora lutea/dam	Mean	10.7	10.8	10.2	12.4
Implantations/dam	Mean	5.8	6.8	5.7	6.2
Live fetuses/litter	Mean	5.0	6.2	5.4	4.4
	%	84.93	85.43	94.68	65.55
Early resorption/litter	Mean	0.7	0.4	0.3	1.5
	%	14.27	12.02	5.32	26.85
Late resorption/litter	Mean	0.1	0.2	0.0	0.1
	%	0.79	2.54	0.0	1.72
Total resorption/litter	Mean	0.8	0.6	0.3	1.6
	%	15.07	14.57	5.32	28.57
Litters with resorptions	Mean	10	9	3	13
	%	55.6	52.9	17.6	76.5
Dead fetuses/litter	Mean	0	0	0	0
	%	0	0	0	0
Non-live implants/litter	Mean	0.8	0.6	0.3	1.6
	%	15.07	14.57	5.32	28.57
Litters with nonlive implants	Mean	10	9	3	13
	%	55.6	52.9	17.6	76.5

Groups: 0= control; 1= 0.0015 mg/kg/day; 2= 0.005 mg/kg/day; 3= 0.1 mg/kg/day

Fetal Parameters:

The numbers of fetuses examined include 91, 107, 92, and 76 from the control, LD, MD, and HD groups, respectively. The fetal weight was decreased at the HD group by gemcitabine treatment. Sex ratio and the percent of fetal runts were not adversely affected.

Fetal malformations were increased due to visceral malformations affecting the cardiovascular, digestive, and excretory systems. Malformations of aorta, pulmonary artery, heart, lungs, gall bladder, and kidney were observed. Skeletal malformations observed at the HD groups included extra sternbrae, fused sternbrae, misshapen sternbrae, extra presacral vertebra, and incomplete ossification of the medial phalanx. No adverse effects were observed in the LD and MD groups.

Fetal parameters from female rabbits given i.v. doses of LY188011 HCl

Parameters		Treatment Groups			
		0	1	2	3
Affected implants/litter	Mean	0.8	0.6	0.5	2.5
	%	15.76	15.41	9.94	39.80
Litters with affected implants	Mean	11	10	6	15
	%	61.1	58.8	35.3	88.2
Litters with live fetuses	Mean	2.4	3.1	2.8	2.0
	%	53.32	47.07	53.70	44.53
Males	Mean	2.6	3.5	2.6	3.0
	%	46.68	52.93	46.30	55.47
Females	Mean	44.71	41.49	44.15	37.60
	%	44.71	41.49	44.15	37.60
Fetal weight/litter (♂+♀)	Mean	0.2	0.4	0.0	0.1
	%	2.42	4.79	0.0	7.62
Fetal runts/litter	Mean	0.9	1.5	1.2	0.0
	%	16.69	19.82	25.94	0.0
Normal fetuses/litter	Mean	0.1	0.1	0.2	0.9
	%	0.69	0.89	5.25	20.47
Fetuses with malformations	Mean	1	1	4	6
	%	5.6	6.3	23.5	40.0
Litters with fetuses having malformations	Mean	0.0	0.1	0.2	0.5
	%	0.0	1.67	9.31	26.92
Fetuses with malformations/litter	Mean	0.1	0.0	0.1	0.6
	%	1.11	0.0	6.25	11.54
Male	Mean	0.0	0.1	0.2	0.5
	%	0.0	1.67	9.31	26.92
Female	Mean	0.1	0.0	0.1	0.6
	%	1.11	0.0	6.25	11.54

Groups: 0= control, 1= 0.0015, 2= 0.005, 3= 0.1 mg/kg/day

TABLE 8 (CONTINUED) DEVELOPMENTAL ANOMALIES IN FETUSES OF FEMALE RABBITS GIVEN INTRAVENOUS DOSES OF 186011 HYDROCHLORIDE, STUDY 800291

MALFORMATIONS *****	TREATMENT GROUP			
	00	01	02	03
EXTERNAL				
ABDOMEN-BODY WALL-VISCERAL ORGANS-PROTRUDING	1(1)A	1(1)	0(0)	0(0)
ABDOMEN-UMBILICUS-INTESTINES-PROTRUDING	0(0)	0(0)	0(0)	4(1)
ABDOMEN-UMBILICUS-TWISTED	0(0)	2(2)	0(0)	1(1)
VISCERAL				
CARDIOVASCULAR SYS-AORTA-PULMONARY ARTERY-FUSED	0(0)	0(0)	0(0)	2(2)B
CARDIOVASCULAR SYS-AORTA-ENLARGED	0(0)	0(0)	0(0)	3(2)
CARDIOVASCULAR SYS-AORTA-TRANSPOSITION	1(1)A	0(0)	0(0)	0(0)
CARDIOVASCULAR SYS-HEART-ATRUM-ENLARGED	1(1)A	0(0)	0(0)	0(0)
CARDIOVASCULAR SYS-HEART-VENTRICLE-ENLARGED	1(1)A	0(0)	0(0)	0(0)
CARDIOVASCULAR SYS-HEART-MISSHAPEN	0(0)	0(0)	0(0)	1(1)
CARDIOVASCULAR SYS-PULMONARY ARTERY-SHALL	1(1)A	0(0)	0(0)	2(2)
DIGESTIVE SYSTEM-GALL BLADDER-ABSENT	0(0)	0(0)	0(0)	4(1)B
DIGESTIVE SYSTEM-GALL BLADDER-REDUNDANT	0(0)	0(0)	0(0)	1(1)
RESPIRATORY SYSTEM-LUNG-LOBE-SHALL	0(0)	0(0)	0(0)	1(1)
RESPIRATORY SYSTEM-LUNG-LOWER LOBE-SHALL	0(0)	0(0)	0(0)	1(1)
RESPIRATORY SYSTEM-LUNG-MIDDLE LOBE-SHALL	0(0)	0(0)	0(0)	1(1)
RESPIRATORY SYSTEM-LUNG-POSTCAVAL LOBE-SHALL	0(0)	0(0)	0(0)	1(1)
RESPIRATORY SYSTEM-LUNG-UPPER LOBE-SHALL	0(0)	0(0)	0(0)	1(1)
URINARY SYSTEM-KIDNEY-DISPLACED	0(0)	0(0)	0(0)	2(2)
SKELETAL				
AXIAL SKELETON-RIB CAGE-STERNUM-SCRAMBLED	0(0)	0(0)	0(0)	1(1)
AXIAL SKELETON-VERTEBRAL COLUMN-CAUDAL VERTEBRA	0(0)	0(0)	1(1)	0(0)
-CENTRUM-FUSED				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-CERVICAL VERTEBRA-ARCH-EXTRA				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-CERVICAL VERTEBRA-ARCH-SHALL				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-ARCH-DISPLACED				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-ARCH-EXTRA				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-ARCH-MISSHAPEN				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-ARCH-SHALL				
AXIAL SKELETON-VERTEBRAL COLUMN	0(0)	0(0)	1(1)	0(0)
-THORACIC VERTEBRA-CENTRUM-FUSED				

E. A Perinatal/Postnatal Study of Gemcitabine HCl given intraperitoneal injections to CD-1 Mice, Study #M19390: (vol. 1.32)

CD-1 pregnant F0 female mice (25/group) were given i.v. injections of gemcitabine at doses of 0, 0.05, 0.25, or 1.5 mg/kg/day (0, 0.15, 0.75, or 4.5 mg/m2/day) on gestation day 15 through postpartum day 20. For the F1 breeding trial, females were cohabited with non-sibling males for up to 2 weeks. F1 generations were separated from males on the day evidence of mating was obtained (gestation 0). Females were permitted to bear the litter and rear their offspring to weaning. Selected offspring were allowed to mature and a mating trial was conducted.

Measurements and Observations:

Daily: survival/signs of toxicity
 Weekly: body weight, food consumption
 Days 30-60: behavioral assessments (pre-, postweaning)
 12-13 weeks: mating, reproductive assessments
 Termination: necropsy of females (day 20 gestation) live/dead fetuses, size, fetal malformations; necropsy of F₀ females and f₁ offspring on postpartum

Results:

Survival and Signs of Toxicity:

All F0 generation females survived and no treatment-related signs of toxicity were observed. During the study, F1 mice one animal from 0.05 and 0.25 mkd group and 4 animals from the 1.5 mkd group died during the first week. All other mice survived until scheduled termination. Clinical signs observed in the F1 generations include rough hair coat, discolored tail, dehydration, alopecia, genital abscess, abrasion, and trauma accompanied by perineal soiling.

Body weight/food consumption:

For F0 generation, decreases (@10%) in maternal body weight and food consumption were observed in dams from the HD group during the first 2 weeks postpartum and during the third week of lactation. No differences in mean maternal body weight, body weight gain, or food consumption were observed in other treatment groups.

Organ Weights:

Dose-related increased spleen weights (14%,LD;34%,MD;83%,HD) and decreased kidney weights <10% were observed in the MD and HD groups. Both absolute and relative thymus (32%, 31%) and uterine weights were decreased @32%.

Reproductive Parameters:

Gemcitabine given during late gestation did not affect reproductive parameters in female mice. All dams were pregnant and delivered viable litters. There were no differences in gestation length (@18 days), live born index (@99.5%), or live litter size.

Progeny Observations and Necropsy Findings-F0 Generation:

Between postpartum days 0 and 21 a total of 23, 7, 7, and 9 pups from the 0, 0.05, 0.25, and 1.5 mg/kg groups were found dead. 17/23 control litters died from cage flooding accident. Pups from 5 litters of the HD group showed small and unthrifty appearance, coolness to touch, and dehydration. These clinical observations were accompanied by extreme growth retardation (@49% of the control mean) on postpartum day 21.

No findings related to maternal gemcitabine treatment were observed in the external, internal and skeletal examinations.

Progeny Measurements F0 Generation:

Maternal treatment with gemcitabine during late gestation and throughout the lactation period did not affect the number of live progeny nor progeny survival during the first 3 postpartum weeks. However, mean progeny body weights were decreased >10% in the MD group on postpartum day 21, and progressively decreased @25% in the HD group during the last 2 weeks of the lactation period.

The early indices of morphological development, pinna detachment and hair appearance were not affected by treatment. Dose-related delays in eye opening were seen on postpartum days 15-17 in the MD and HD groups.

Prewaning Behavioral Assessment-F1 Generation:

During the preweaning period, no differences were observed in negative geotactic performance on postpartum days 5 through 7 for the F1 progeny from the control and gemcitabine treatment groups. Both males and females showed a normal developmental pattern of performance.

Postweaning Behavioural Assessments-F1-Generations:

At 30 and 60 days of age, activity levels of F1 animals were monitored. Reactivity and auditory function of F1 animals were measured in the startle habituation procedure. There were no significant effects of maternal treatment on the startle response in these animals.

Mating Performance and Fertility-F1 Generation:

There were no treatment-related effects on precoital periods or on the F1 fertility indices: 96%, 100%, 92%, and 94% of the females were pregnant from the 0, 0.05, 0.25, or 1.5 mg/kg/day

treatment groups, respectively.

No significant changes in hematology or gross pathology were reported in F0 dams or in F1 generation animals.

Summary of Reproductive Toxicology:

In a Segment I male fertility study, i.p. doses of 0.05 mg/kg/day or 3.5 and 10 mg/kg/week were given. At 3.5 and 10 mg/kg/week, minimal to moderate decreases in spermatogenesis resulted. The 0.5 mg/kg/day caused severe hypospermatogenesis, decreased fertility and decreased implantations.

In a Segment I female fertility study, LY188011 had no effect on female fertility at i.v. doses of 0, 0.05, 0.25, or 1.5 mg/kg/day gemcitabine for 2 weeks prior to cohabitation with untreated males. No treatment related effects were seen on precoital periods, mating performance, or fertility. Maternal toxicities included decreased body weight and changes in erythrocytic parameters and increased spleen weights at the HD. Reproductive and developmental toxicity in the HD group included decrease in fetal viability and developmental delays (fetal weight, incomplete ossification).

The segment II teratogenic effects of gemcitabine were studied in mice given i.v. doses of 0, 0.05, 0.25 or 1.5 mg/kg/day on gestation days 6 through 15. Gestational treatment with gemcitabine produced dose-related decreases in body weight, increases in spleen and thymus weights during gestation. The proportion of fetuses with malformations was slightly increased in the HD group. An increase incidence of cleft palate in the HD group contributed to the significant increase in malformations. Digital malformations were slightly increased in the HD group. About one-half of the malformed fetuses in the HD groups were classified as runts.

In the postnatal segment of the study, gestation length was slightly increased (18.8 day), the number of females delivering liveborn litters, liveborn litter size, live litter size, preweaning body weight, and progeny survival were reduced in the HD group. General morphology of the surviving offspring were not affected by maternal treatment with gemcitabine.

The segment II teratogenic effects of gemcitabine were determined in rabbits given i.v. doses of 0, 0.0015, 0.005 or 0.1 mg/kg/day on gestation days 6 through 18. There were no adverse effects on body weight gain or food consumption. The treatment-related maternal toxicity in the rabbit were slight decreases in RBC count, Hb and PCV. Gemcitabine developmental toxicity was demonstrated by decreased fetal weight and fetal viability and increased incidence of malformations (visceral and skeletal) in the HD group. Visceral anomalies included cardiovascular, digestive, excretory organ malformations. Skeletal malformations included sternbrae (extra, fused, misshapen), extrapresacral vertebra, and incomplete ossification of the median phalanx.

In a Segment III perinatal/postnatal study, daily i.v. doses of gemcitabine at 0, 0.05, 0.25, or 1.5 mg/kg/day to female mice during late gestation and throughout a 3 week lactation period produced a decreased in maternal body weight and food consumption in the HD group. Reproduction parameters and progeny survival to weaning were not affected by gemcitabine. Dose-related decreases in progeny body weights and retarded physical development resulted in the HD group. Body weights of the surviving F1 animals recovered to normal by 4 to 7 weeks of age. Females from the HD treatment group were less active than controls at 30 days of age. No other treatment-related changes in F1 generation survival, behavioral or reproductive performance were noted.

VI. Mutagenicity Studies:**A. The effect of Gemcitabine (LY188011) HCl on the induction of reverse mutations in Escherichia Coli using the Ames test, Study No. 910430AMS2499: (vol. 1.33)**

LY188011 concentrations of 250, 500, 1000, 2000, and 5000 ug/plate with or without metabolic activation were tested in E. Coli strain WP2uvrA-. The positive controls (ENNG, and 2AA) and the negative vehicle control (water) were used.

Results indicated that LY188011 did not induce E. Coli revertants when tested at concentrations up to 5000 ug/plate in both activated and non-activated assays. Gemcitabine was not mutagenic in the Ames E. Coli mammalian microsome test for bacterial mutation.

B. The effect of Gemcitabine HCl on the in Vitro Induction of Chromosome Aberrations in CHO cells, Study No. 910424CAB2499 and 910530CAB2499: (vol. 1.34)

Gemcitabine concentrations of 0.005, 0.01, 0.03, 0.05, and 0.07 ug/ml without metabolic activation, and 0.01, 0.04, 0.07, 0.1, and 0.13 ug/ml with metabolic activation were tested in CHO cells for the chromosomal aberration assay. Cells from CHO cultures were exposed to gemcitabine for 4 hrs. The positive controls were used: Mitomycin C served as the positive control in the nonactivated assay, and cyclophosphamide as the positive control in the activated assay.

Results: No significant increase in the number of cells with aberrations were observed with or without metabolic activation in cultures treated with gemcitabine compared to solvent control. Cultures treated with positive controls, Mitomycin C and cyclophosphamide, produced 60 and 48% aberrant cells, respectively, indicating that the test system was sensitive for the detection of a direct-acting clastogenic agent.

C. The effect of Gemcitabine HCl on the in Vivo Induction of Micronuclei in bone marrow of ICR mice, Study No. 910625MNT2499: (vol. 1.34)

I.V. doses of 0, 0.1875, 0.375, or 0.75 mg/kg gemcitabine was administered for 2 consecutive days to ICR mice. Positive and negative controls were used. Approximately 24 hr after second treatment with gemcitabine, bone marrow was collected, and the frequency of micronucleated polychromatic erythrocytes (MPCE/1000PCE) was determined microscopically.

Results: The mean incidence of MPCE in males was 2.2, 3.6, and 4.4/1000 PCE for males and 3.4, 3.4, and 7.0 for females treated with gemcitabine. Mean incidence of MPCE for the solvent control was 1.0 for males and 0.4 for females. The increases in MPCE in gemcitabine treated males and females were statistically significant indicating that gemcitabine induces micronuclei in bone marrow of ICR mice.

VI. Mutagenicity Studies: Mouse lymphoma assay; Sister chromatid exchange;
Chromosome aberration; Micronucleus test

Comment:

The NDA submission appears to be complete from the standpoint of pharmacology/
toxicology requirements. This application is fileable.



Doo Y. Lee Ham, Ph.D.

cc: Original NDA 20-509
HFD-150/Division File
/LeeHam
/DeGeorge
/Schechter
/CSO
DYLH/WP

To: Ms Lily Zahed 1-(317)-277-1801
Dr. Kelly Freeman 1-(317)-276-1337
Eli Lilly and Company

From: Sue-Jane Wang, Ph.D.
Genny Schechter, M.D.
Steve Wilson, Ph.D.
DOPDP, FDA

Topic: Additional needed information for Gemcitabine NDA# 20509

Date: June 12, 1995

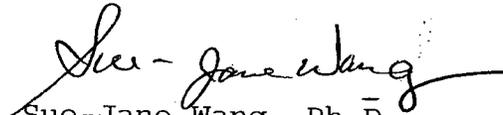
In the fax regarding data request sent to you on June 9, 1995, please also include the beginning and ending dates of the clinical benefit response, and the corresponding duration of clinical benefit response.

Following requests are related to the repeated observations per patient.

For all patients, please provide, in electronic form, the trial ID (e.g., JHAY), the investigator ID, the weekly measurements of the pain intensity, the analgesic consumption, the performance status, and the weight (please give me a call regarding a proper form of the data file).

Prior to the submission, please test your electronic file to assure that they will load on the DOS-based system running SAS6.08.

As the review time is running short, please expedite this request. I can be reached at 1-(301)-594-5764. We look forward to hearing from you soon.


Sue-Jane Wang, Ph.D.

cc: Robert Justice, M.D.
File

*cc: Original # NDA 20509
HSD-150 / Dist. to
NDA-150 / MD - ~~HSD~~ Schechter
HSD-150 / CSD - McC*

To: Ms Lily Zahed 1-(317)-277-1801
Dr. Kelly Freeman 1-(317)-276-1337
Eli Lilly and Company

From: Sue-Jane Wang, Ph.D.
Genny Schechter, M.D.
Steve Wilson, Ph.D.
DOPDP, FDA

Topic: Additional needed information for Gemcitabine NDA# 20509

Date: June 9, 1995

Thank you for your most recent phone response regarding the questions faxed to you on June 7, 1995. Reference phone call with Ms Zahed: there are still several things we require.

(1) For all patients, please provide, in electronic form, the basic patient demographic information, the trial ID (e.g., JHAY), the investigator ID, the best tumor response and the last tumor response. Also provide the actual dates (SAS date format) for dates of: randomization, best tumor response, progressive disease (PD), death, removal for toxicity and last follow-up (LFU); the censoring indicators of disease progression and survival; the duration of the tumor response, the time to disease progression, and the survival time. For those variables where codes were used, please provide the SAS formats.

(2) With regards to the clinical benefit response, please provide, in electronic form, for all patients an aggregated code of the Karnofsky Performance Status, pain intensity, analgesic consumption, and weight (per protocol). If additional variable(s) were used in the clinical benefit response derivation, please also include them.

(3) Please provide the equation used to classify an individual as a clinical benefit responder and the final clinical benefit response for each patient.

The above requests should contain one observation per patient. A request for data including repeated observations per patient will be discussed in the near future.

Prior to the submission, please test your electronic file to assure that they will load on the DOS-based system running SAS6.08.

As the review time is running short, please expedite this request. If you have any question, please do not hesitate to call me at 1-(301)-594-5764. We look forward to hearing from you soon.

Sue-Jane Wang
Sue-Jane Wang, Ph.D.

cc: Robert Justice, M.D.
File

*cc: Original NDA 20509
HEID 1501 Qui File
HEID 1501 MO-Schechter
HEID 1501 280 - Maly*

To: Ms Lily Zahed 1-(317)-277-1801
Dr. Kelly Freeman 1-(317)-276-1337
Eli Lilly and Company

From: Sue-Jane Wang, Ph.D.
Genny Schechter, M.D.
Steve Wilson, Ph.D.
DOPDP, FDA

Topic: Additional needed information for Gemcitabine NDA# 20509

Date: June 9, 1995

Thank you for your most recent phone response regarding the questions faxed to you on June 7, 1995. Reference phone call with Ms Zahed: there are still several things we require.

(1) For all patients, please provide, in electronic form, the basic patient demographic information, the trial ID (e.g., JHAY), the investigator ID, the best tumor response and the last tumor response. Also provide the actual dates (SAS date format) for dates of: randomization, best tumor response, progressive disease (PD), death, removal for toxicity and last follow-up (LFU); the censoring indicators of disease progression and survival; the duration of the tumor response, the time to disease progression, and the survival time. For those variables where codes were used, please provide the SAS formats.

(2) With regards to the clinical benefit response, please provide, in electronic form, for all patients an aggregated code of the Karnofsky Performance Status, pain intensity, analgesic consumption, and weight (per protocol). If additional variable(s) were used in the clinical benefit response derivation, please also include them.

(3) Please provide the equation used to classify an individual as a clinical benefit responder and the final clinical benefit response for each patient.

The above requests should contain one observation per patient. A request for data including repeated observations per patient will be discussed in the near future.

Prior to the submission, please test your electronic file to assure that they will load on the DOS-based system running SAS6.08.

As the review time is running short, please expedite this request. If you have any question, please do not hesitate to call me at 1-(301)-594-5764. We look forward to hearing from you soon.

Sue-Jane Wang
Sue-Jane Wang, Ph.D.

cc: Robert Justice, M.D.
File

*cc: Original NDA 20509
HEID 1501 Div File
HEID 1501 MO-Schechter
HEID 1501 80 - M&B*

Division of Oncology Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Labeling Review

APR 16 1996

April 16, 1996

NDA: 20-509

Date of Submission: March 18, 1996, and FAX dated: 4/8/96
Received by Reviewer: April 5, 1996, and FAX dated 4/8/96

Applicant: Eli Lilly and Company
Indianapolis, IN 46285

Drug Name: Gemzar (Gemcitabine Hydrochloride; dFdC)

Material Reviewed: Revised Draft Labeling dated 3/18/96; Lilly's response to the draft labeling

Comment:

The applicant has revised the pharmacologic portion of draft labeling as we recommended except item #4 and item #6. For the item #4 on the last note p.52, sponsor has revised the fraction of the recommended human dose that was given to rabbit to 1/600. We accept the factor of 16 (Km) for 4 kg rabbit by the following calculation:

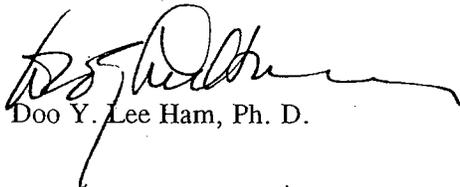
The body weight of NZW rabbit is ~4 kg, and the K value of rabbit is 10, $Km = (10^2 \times W(\text{kg})^{1/3})/K$

$$Km = (10^2 \times 4^{1/3})/10 = 15.874 = 16$$

For the item #6 on p.54, sponsor responded that in the Overdosage section of the labeling should reflect human data, for the human data are much more pertinent than animal data for gemcitabine. The clinical reviewer will comment on this item #6.

Recommendation:

The revised labeling is approvable with regard to the pharmacologic portion of the NDA.


Doo Y. Lee Ham, Ph. D.

cc: Orig. NDA 20-509
HFD-150/Division File
/LeeHam
/DeGeorge
/Schechter
/CSO

DYLH/WP



Pharmacological and Toxicological Review of IND 29653

Review # 2

Date of submission:4/13/87

REceived by the reviewer:4/28/87

Date of Review completed:5/6/87

DRUG: LY188011 HCl
SPONSOR: Lilly Research Laboratories
DRUG CATEGORY: antineoplastic agent.

SUBMITTED MATERIALS: Preliminary data on studies M00685, D02085,
and the HSV-1 study in mice.

3-week ip preliminary toxicity study in mice:

No. of animals: 5/sex/group.

Dose levels:

treatment group	dose(mg/kg)	frequency of dosing/wk
0	0	7
1	1	7
2	5	2
3	10	2
4	30	2
5	60	1

Mortality: none (one mechanical death)

Body weight:normal

Signs of toxicity: none.

Hematology: Decreases in leukocyte counts and erythrocytic parameters were noted in all drug-treated groups.

Clinical Chemistry: Increase in AP in all male groups except for the lowest dose group.

Pathology: The only pathologic change was inhibition of spermatogenesis and degeneration of the testes in all groups.

Based on these results, dose levels and dose schedules were selected for the study in mice (see original submission).

3-week iv preliminary toxicity study in dogs:

No. of animals:1/sex/group.

Dose level:

Treatment groups	dose(mg/kg)	frequency of dosing/wk
1	3	2
2	6	2

Mortality:none; however, severe hematologic toxicity prevent the study from going beyond the 3rd week (see "hematology" below).

Toxic sings: The low-dose female and the high-dose male developed suppressed appetite and weight loss during the second week of the study. Both dogs had loose stools on the third day of the study.

Subsequent Pharmacological Review of IND 29653
Review # 3

Date of Submission: 5/18/87, received by HFN-150
on 5/22/87

Date of Review Completed: 8/12/87

SPONSOR:

Lilly Research Laboratories
Eli Lilly and Co.

DRUG:

Compound LY188011 Hydrochloride

DRUG CATEGORY:

Antineoplastic agent.

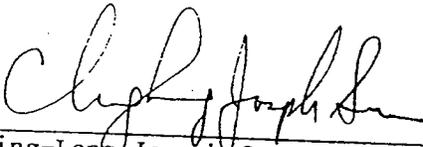
MATERIAL REVIEWED:

" The effect of LY188011 on the in vivo induction of sister chromatid exchange in Bone marrow of Chinese Hamsters, Toxicology Report No. 9". Performed by the sponsor.

Chinese hamsters were treated ip with 50, 25, and 12.5 mg/kg of LY188011 in the 1st study and 12.5, 6.25, and 3.125 mg/kg in the 2nd study. 12.5 mg/kg of cyclophosphamide was administered ip to animals of the positive control group. The induction of SCE was scored for all test animals 19 hr following treatment.

Results: In the 1st study, the bone marrow cells could not be scored for SCE induction since they produced extreme cytotoxicity. The frequency of SCE formation in the drug-treated animals of the 2nd study was not different from control. Thus, it did not induce SCE in vivo in bone marrow of Chinese hamster.

RECOMMENDATION: NAI.


Ching-Long Joseph Sun Ph.D.

2058E

cc:

Orig. IND 29,653 ✓

HFN-150/Div. File ✓

HFN-150/CJSun

HFN-150/CSchumaker

HFN-340

HFN-150/KE

Ryoin Paper
8/13/87

Hematology: Both high-dose animals have a greater than 50 % (one of them was 67%) reduction in leukocytes on test day 6. All animals had a 50% reduction on day 13. One high-dose on test day 7 and all dogs on day 14 were not given the scheduled dose because of leukopenia which might be incompatible with survival. Some degrees of reversibility of leukopenia were noted. There was a decrease in the thrombocyte in the two high-dose dogs.

Clinical Chemistry: Except for a few changes (details were not provided) in the low-dose female at one time period, there were no alterations according to the sponsor.

Pathologic findings: Inhibition of spermatogenesis was the only evidence of toxicity. According to the sponsor, the bone marrow was in an active proliferative state. However, based on severe leukopenia, bone marrow should also be a target organ of toxicity.

Preliminary results on the evaluation of the antiviral activity in mice:

HSV-1:

Dose group and animal no: a daily schedule x4

Study #1: 0, 0.5, 1, 2, or 4 mg/kg i. p.

Study #2: 0, 2, 4, 8, 16, or 32 mg/kg i. p.

Results: The sponsor stated that the drug had no unusual toxicity in the tests due to the various drug treatment groups died with the same median survival time as those in the infected control groups. However, by looking at the Table XII, median day death for control and 32 mg/kg -treated groups are 5.3 and 4.2 days, respectively. The sponsor should provide a statistical analysis to conclude the result.

Pseudorabies virus:

Ten animals per dose groups (20 mg/kg ip, x1 or x2) were studied. Some antiviral activity was observed when the drug was administered as a single dose three hours after viral infection on days 1 and 7.

EVALUATION AND COMMENTS:

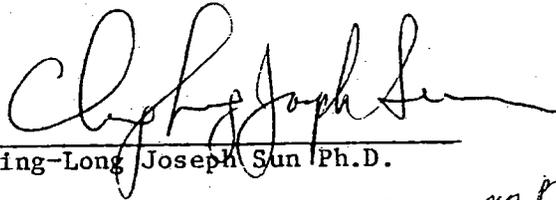
Dogs are more sensitive than mice to the toxicity of LY188011 HCl. Although dogs tolerated well a dose of 60 mg/m² (3 mg/kg/week, see original submission), the dogs at the next higher doses (3 or 6 mg/kg twice a week) encountered severe leukopenia which might be incompatible with survival. Thus, a lower starting dose of 10 mg/m² might provide reasonable safety margin.

There was a discrepancy in the doses of the preliminary dog study between the current submission and the telephone conversation (2/17/87) in which 3mg/kg twice weekly and 6 mg/kg/week were mentioned by the sponsor (Dr. Todd).

The submission of the preliminary antiviral study did not revealed a complete toxicity of the compound in mice since only mortality was monitored. A complete data of antiviral study in gunea pigs should also be provided by the sponsor(see original review).

The sponsor ^{it was stated} should be informed to correct a mistake on page 1390 where dogs tolerated well a dose of 120 mg/m² ~~was mentioned~~. Instead, it should be 60 mg/m² (3mg/kg, see original review). _{once per week}

As stated on page 1397, the sponsor will use normal saline solution as the diluent.



Ching-Long Joseph Sun Ph.D.

1018E

Study may proceed at
the recommended lower
starting dose.
d. prill
6/4/87

Pharmacological and Toxicological Review of IND 29653

Original Review

Date of Review Completed: 3/26/87

Diu

SPONSOR:

Eli Lilly and Co.

DRUG:

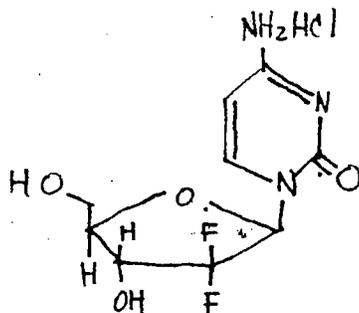
Compound Ly 188011.HCl

Chemical name: 2',2'-difluorodeoxycytidine.
HCl, LY264368.

Formula: $C_9H_{12}ClF_2N_3O_4$

Molecular weight: 299.66

Structural Formula:



DRUG CATEGORY:

Antineoplastic agen.

PORPOSED DOSE LEVEL: The drug is provided as the HCl salt. The doses are expressed in mg of base (LY188011).

Starting dose: 20 mg/m² iv weekly

Escalation #1: 30 mg/m² iv weekly.

Escalation #2: 45 mg/m² IV weekly

Further escalation will continue at 25-50 % increments.

PROPOSED CLINICAL STUDY:

The purpose of the study are (1) to determine the MTD and the relationship between dose and toxicity for LY 188011 administered once weekly iv, and (2) to investigate the side effects attributable to IV LY 188011.

Histological proof of malignancy (solid tumor or lymphoma) refractory to conventional forms of treatment in patients who are not candidates for protocol treatment of higher priority. Patients must be at least 18 years old. No. of patients: 30.

Duration of study: 6 months. A minimum of six weeks of treatment is required.

PHARMACOLOGY AND TOXICOLOGY STUDIES:

Pharmacology:

Antitumor activity: In vivo antitumor activity was conducted in several tumor models. Initial evaluation using daily schedule was disappointing. Good antitumor activity and reduced toxicity was observed when the drug was on an every third day schedule. The summary of antitumor activity against several in vivo tumor models is listed as follow:

Tumor model	Dose level (mg/kg, ip)	ILS (%)	% of inhibition in tumor growth	Optimal dose (mg/kg)
L1210	1.25-20, 1-5-9	68		20
P1534J lymphatic leukemia	1.25-20, 1-5-9		92	20
CA-755 Adenocarcinoma, SAA			94*	20
6C3HED lymphosarcoma, SAA			95	20
P388 lymphatic leukemia	SAA	70		20
X5563 plasma cell myeloma	SAA		100	20
CA-755 denocarcinoma, 2.5-30, 1-4-7-10			100	15
X5563 plasma cell myeloma	1.25-40, SAA		100	40
P388 leukemia, SAA		93		20
L1210	SAA	162		40
B16 melanoma	SAA		77	40
M5 ovarian carcinoma	SAA		99	20
CX-1	10-160, 1-4-7-10-13		76	160
EJ-RAS	SAA		84	160
LX-1	SAA		79	160
LX-1	5-40, 1-3-5-7-9-11-13		94	40
MX-1	5-80, SAA		92	80

SAA: same as above.

In vitro CCRF-CEM human leukemia cell culture assay:
IC 50 of the compound is 1 ng/ml. The comparable 5-methyl analog (198792) is 300-fold less potent and uracil analog (198791) is about 5000-fold less active. The thymidine derivative is almost inactive.

Antiviral activity: It demonstrated antiviral activity against both RNA and DNA viruses using cell culture assays such as HSV-1, PV, Poliovirus-1, influenza-A, parainfluenza-3 and Rhinovirus-3. Antiviral activity against FLV(Friend leukemia virus) was demonstrated with almost complete inhibition of spleen enlargement following iv administration of 30 mg/kg. The in vivo antiviral activity was evaluated against HSV-1 in mice. Studies with treatment schedules of four ip injections with dosage from 0.5-32 mg/kg failed to demonstrate any antiherpes activity. In addition, a single ip administration (6-100mg/kg) of the compound, again, did not show any antiviral activity. In guinea pig, dermal HSV-1 and intravaginal HSV-2 procedures were used. The compound (0.5-2%) was very toxic; thus, it was not developed as a useful antiviral drug. The sponsor should provide a complete toxicity report of the studies.

Inhibition of cell proliferation: LY188011 has been shown to inhibit proliferation at the early S phase of cell cycle. This may indicate a mechanism of action different from that of Ara-C (mid to late S phase).

Pharmacokinetics:

Mice:

Plasma level: Male mice were given an ip dose of LY188011 of 30 or 60 mg/kg . Plasma peak levels were reached at 5 minutes after the doses. The T_{1/2} was 10.4-11.3 minutes (T_{1/2} was 7-13 minutes following iv administration of 20 mg/kg). The major metabolite (O-deaminated) of the compound was 198791. Peak levels were obtained 2-5 minutes after dosing. T_{1/2} was about 50 minutes. plasma concentration of LY188011 increased in proportion to the dose (1-60 mg/kg ip). Both LY188011 and 198791 were excreted in the urine with most being excreted within two hours after dosing. LY188011 is extensively metabolized in the mouse. over a 24 hr period 26.9-29.8% and 38.5-43.5 % of the dose were recovered as LY188011 and 198791, respectively. The glucuronide conjugates were present in urine. Total recovery during the 48 hrs averaged 93.5%.

Disposition: Tissues containing the highest amount of radioactivity were the spleen, thymus, testicles, kidney, femur, small intestines, and lymph nodes. Tissue t_{1/2} was about 0.75-2.96 hr after iv administration of 20 mg/kg..

Fischer 344 rats:

Plasma level: Male rats were given 10 mg/kg iv. Peak levels were observed one minute after dosing. T_{1/2} was 68 minutes. The major route of excretion was in the urine with 78.3 % of the dose recovered. Fecal excretion accounted for 3.54% of the dose. Parent compound was the predominate urinary excretion product. The O-deaminated moiety was the major metabolite with small amounts of the gluconides present. Tissues uptake was rapid. The tissues containing the greatest amount of radioactivity were the thymus, kidney, lymph nodes, and spleen. The T_{1/2} of radioactivity in plasma was 1.8 hr. Tissue half-lives were 1.93-5 hrs. The cytidine deaminase pathway appears to be less active in the rat than in the mouse. After oral administration, the peak plasma levels were reached at 60-90 minutes. Bioavailability of 65.9% was reported.

Tissue distribution to tumor bearing mice were studied. High radioactivity were observed in spleen, lymph nodes, kidney, thymus and tumor (x-5563 tumor cells inoculated s.c.).

Dogs: In the dog following in administration of 14 C-LY188011, 85% of the IV dose was recovered in urine with 3.5% in the feces. In the urine deaminated matabolit predeominated with gluconides present. The half-life of LY188011 in plasma was 1.7hr. It appears that the dog is between the mouse and rat in the metabolic activity. The tissue disposition pattern was not submitted in the IND.

Other pharmacology studies:

Effects on urine electrolytes:

Doses of 0,3,15, or 30 mg/kg of compound LY188011 HCl were administered ip. The results indicated that the compound had no important effects on urine output or electrolyte excretion.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-509

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

RECORD OF FACSIMILE TRANSMISSION

DATE: February 14, 1996

IND/NDA: NDA 20-509

PRODUCT(S): GEMZAR

Transmission sent to: Dr. Kelly Freeman, Eli Lilly Reg. Affairs

Phone/FAX: (317) 276-1337 /fax (317) 276-1652

Subject: Comments and deficiencies from the Medical and Pharm-Tox reviews of the original NDA 20-509.

CLINICAL COMMENTS:

1. In the Overall Safety Review Section, information about drug toxicity is reported by number of cycles but not by dose range/cycle. The median total dose (in mg/m^2) and the range of total dose as well as the median dose (mg/m^2) per cycle and range of dose per cycle (in mg/m^2) for each cycle, the number of patients at risk, and the drug related toxicity grading and treatment emergent signs and symptoms for these different dose ranges should be correlated. Since the clearance of this drug is reduced in the elderly and in women, the number of treatments/cycle is variable, and dosage reductions occurred in many patients a dose/toxicity correlation is needed to accurately define Gemcitabine's toxicity profile.

Additional information must be provided to show that a dose of $1000 \text{ mg}/\text{m}^2$ weekly three out of four weeks is safe in the elderly, especially in elderly women, since the clearance of drug is markedly reduced in this population. Please provide more information on the number of elderly men and woman exposed to drug, the total dose to which each patient was exposed, the dosing schedule on which the patient was treated, the toxicities observed by total dose, and information on dose reductions due to toxicity in subsequent cycles of therapy in this age group.

2. In the Clinical Studies Section:

- a. Sentence three, paragraph one should be changed from _____
_____ " to _____

FU or FU containing regimens. " In the protocol for JHAY no "allowed" FU regimens were specified.

- b. Sentence one, paragraph two which reads _____

- c. The sentence in section ii) which reads _____

_____ **"the patient was stable on all of the
aforementioned parameters, and showed a marked, sustained weight
gain (~7% increase) not due to fluid accumulation.** " The sponsor has
not provided data to prove that caloric intake was increased and has
not proved that weight gain due to increased caloric intake occurred
in the clinical benefit responders in any trial in this NDA.

- d. In the third paragraph of the Clinical Studies section the following
sentences should be changed from : _____

- e. In Table 3 on page 6, the following changes should be made:
- i. The _____
deleted from the table _____
 - ii. The _____
deleted from the table _____

- _____
- iii. _____
- iv. Median Time to Progressive Disease should be changed to the following:
 - (1) Gemcitabine -- median TTP - 65 days (Range:0 - 288 days)
 - (2) FU -- median TOP -29 days (Range:0 -365+ days)
- v. Time to Treatment Failure should be changed to:
 - (1) _____
 - (2) _____
- vi. _____ should be deleted from the table since an Eli Lilly sponsored independent review board could not confirm any objective tumor responses on either arm. [After review of the radiographic data by the agency, two partial response(s) were identified in JHAY, both on the FU arm.]

f. In the next paragraph the following sentences:

must be amended since objective evidence of progression while on FU was not provided to confirm FU refractoriness. The sentence might be better worded as follows:

g. In Table 4, the following changes should be made based on the statistics done by the agency:

i. _____

ii. _____
iii. _____
iv. _____

v. _____

vi. _____

vii. _____

h. The following sentences should be revised:

Objective information should be provided in the label with regard to the number of patients at risk, the number of patients demonstrating qualitative symptomatic improvement, the duration of the symptomatic improvement, and the objective response rates (CR and PR) seen in the Phase II trials in pancreatic cancer patients.

3. In the Indications and Usage Section:

The following sentence: _____

4. In the Warnings Section, a statement should be added about the possibility of Hemolytic-Uremic Syndrome particularly in patients with preexisting renal impairment.

5. In the Laboratory Tests Subsection, a phrase indicating that renal and hepatic function should be evaluated prior to initiation to therapy with Gemcitabine should be included.

6. In the Precautions Section, the following changes are necessary:
 - a. The pregnancy category is incorrect. See pharmacology review.

 - b. A section entitled Drug Interactions needs to be included with information provided about recognized drug interactions, if known. (See Biopharm comments.)

7. The Adverse Reactions Subsection, as written, does not accurately describe the toxicities of Gemcitabine. The information contained in this section can not be verified from the NDA. The following information should be included in this section in tabular form:
 - a. A table must be included which lists all the common toxicities which were graded using the WHO Common toxicity criteria and reported for Gemcitabine, the number of and % incidence of each of these toxicities in the 979 patients treated on the weekly schedule, the number of and % incidence of the same toxicities in the 244 pancreatic cancer patient data base along with the number and % incidence of Grade III/IV toxicity in this population. _____

 - b. A brief narrative about specific toxicities must include information about how the overall incidence of each toxicity (number / number at risk, %) and the % with each grade of toxicity were determined. Continue to include in the narrative a description of study

discontinuations and life threatening adverse reactions.

8. In the Adults Subsection, delete paragraph 4 which reads _____

9. In the Elderly Patients Subsection, provide evidence to prove that Gemzar® is well tolerated in the elderly by relating total dose mg/m² with the occurrence of toxicity. The data provided in the NDA is not adequate to determine if Gemcitabine, at the dose recommended in the label, is safe in the elderly. Information must be provided about the total dose per cycle, number of dose reductions or missed doses per cycle, and total dose of drug in mg/m² administered in patients > 65 as compared to patients age 65 or less. Analyses which relate total dose, doses per cycles, and degree of toxicity should be provided by sex and age (males ≤65, males >65, females ≤65, females >65) since clearance is markedly reduced in females and patients greater than age 65.
10. The Subsection title : _____ should be retitled Pediatric Patients in keeping with the regulations.
11. In the References Section, references no. _____ should be deleted.

PHARMACOLOGY-TOXICOLOGY COMMENTS

Labeling:

Labeling generally conforms to the format specified under 21 CFR Part 201, Subpart B, dated April 1, 1994. The proposed labeling describes the preclinical observations for the most part. However, the following revisions are requested:

1. Under the Clinical Pharmacology Section on p. 2, delete _____

2. Under Clinical Pharmacology on p. 3, the last portion of the first paragraph should read to: "In CEM T lymphoblastoid cells, Gemcitabine induces internucleosomal DNA fragmentation, one of characteristics of a programmed cell death." Delete the following sentence beginning, _____

-
-
3. Under the Precaution Section on p. 10, Carcinogenesis, Mutagenesis, Impairment of Fertility Section, the paragraph should be replaced and should read:

"Carcinogenesis: Long-term animal studies to evaluate the carcinogenic potential of _____ have not been conducted.
Mutagenesis: Gemcitabine induced forward mutations in mouse lymphoma (L5178Y) cell assay *in vitro* and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested in Ames assay, sister chromatid exchange assay *in vivo*, chromosomal aberration assay *in vitro*, and did not cause unscheduled DNA synthesis assay *in vitro*. **Impairment of Fertility:**

4. Under the Pregnancy Category Section on p. 10: Pregnancy Category 'C' should be changed to 'D'. The beginning paragraph should read:

"Gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic and _____ fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice, and fetotoxic causing fetal malformation (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/200 and 1/900 the recommended human dose on a mg/m² basis, respectively). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays." There are no studies of Gemcitabine in pregnant women

5. Under the Precaution Section, information about possible dermal absorption should be included for handling of Gemcitabine while in solution. In acute dermal irritation study, no dermal irritation was seen. However, 2/3 rabbits exhibited drug-related systemic toxicities (deaths, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

6. Under Overdosage, the beginning paragraph should be changed to:

If you have any questions or comments, please contact Linda McCollum, CSO, at (301) 594-5771.



Linda McCollum, CSO

February 15, 1996

*Cl Original NDA-20-509
HFD-150/Dev File
HFD-150/CSO - mcb*

Lilly

Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

March 13, 1996

ORIGINAL



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150
Attn: Document Room, 3rd Floor
1451 Rockville Pike
Rockville, Maryland 20852-1448

**Re: NDA 20-509--Gemzar (gemcitabine HCl)
Amendment to NDA**

ORIG AMENDMENT

(BZ)

Please find enclosed an amendment to the Gemzar NDA. This amendment is being submitted in response to your FAX communications of February 14, 1996 (2 separate communications on this date) and February 20, 1996.

We have provided 5 additional desk copies of Volume 1 and 2 additional desk copies of Volume 2 (Attachments). Please contact us if further copies are required.

In order to facilitate resolution of any remaining questions, please feel free to contact Dr. Kelly Freeman by telephone at 317-276-9596 or by digital pager at _____
_____. Additionally, if you have no objection, we would like to contact you weekly on Thursdays, beginning March 21, 1996, to confirm that no new concerns have arisen and/or that no additional data is needed.

Please call me at 317-277-1324 if there are any further questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

A handwritten signature in black ink that reads "Timothy R. Franson M.D." with a stylized flourish at the end.

Timothy R. Franson, M. D.

Executive Director

North American Regulatory Affairs

Enclosures

TRF:dmm

RECORD OF FACSIMILE TRANSMISSION

Date: March 27, 1996

IND/NDA: NDA 20-509

Product(s): Gemzar (gemcitabine HCL)

Facsimile sent to: Dr. Kelly Freeman, Eli Lilly Res. Labs, Regulatory Affairs

Phone/FAX: (317) 276-1337 /fax (317) 276-1652

Subject: Deficiencies for microbiology review of submissions July 26, 1995 and January 9, 1996.

Reference is made to your New Drug Application dated February 1, 1995 and its amendments dated April 17, 1995, July 26, 1995 and January 9, 1996 for GEMZAR, NDA 20-509. The submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed. Please provide an amendment to address the following concerns.

1. Concerning drug solution bioburden:
 - a. Please provide specifications (limits) for bioburden content in solution bioburden prior to filtration.
 - b. We note that the bioburden test method (BO1227-001, 17 April 1995 amendment) includes addition of 2'-Deoxycytidine HCl in a pH 8.0 buffer onto the filter and SCDM agar prior to incubation. Why is the additive in an alkaline buffer when the drug solution is acidic (pH 2.0 to 3.0)? Would this not cause a pH shock to the organisms being recovered? Is the 0.1 mL of 20 mg/mL drug substance significant when the amount of agar medium dilutes its strength? How much agar medium is in the plate?
2. We refer to the described solution filtration validation tests for both manufacturing sites (26 July 1995 amendment, pages 42, 43, 66 and 67).
 - a. Concerning, the determination of the bubble point after the exposure of the filter to the drug solution, was the bubble point determined using drug solution or water to wet the membrane? Were bubble point values determined before and after drug solution contact? Please summarize your data.

March 27, 1996

- b. What were the bubble point values for the tested filters and were these near the minimum bubble point specified for filters used in manufacture?
 - c. We note the evaluation of extractables used water because the drug is aqueous. However, the drug is also acidic (pH 2.0 to 3.0). Has the effect of the acidity on the filter (medium and cartridge) been considered?
 - d. The manufacture process specification for pressure and duration of the filter process were not noted. The pressure used during validation experiments was not noted. The pressure specified during manufacturing should be less than the pressure used during validation. Manufacturing instructions should state these pressures.
3. We refer to the tests which challenge the integrity of the container and closure system of the drug product (9 January 1996, pages 1065 - 1068).
- a. The description of the test methods and results did not include the titer (count) of the challenge microorganisms.
 - b. The use of spores in microbial challenges of a container seal is not viewed as a significant challenge since spores are large and are not motile (small motile microbes are the more conventional microbial challenge). However, this view is in part due to the absence of descriptions of positive controls with "breached" closures (page 1067). The way the positive controls were conducted is critical to evaluating the test's appropriateness. Please describe the test's controls (including the method of breaching containers) and provide summarized results.
 - c. The vial described for use in the 1 gram product strength manufactured at Fegersheim was specified as _____ 26 July 1995, page 61). This is a different specification from the vial specified for use in Indianapolis, and is different from the vial addressed in the container and closure integrity tests. Please clarify this.

March 27, 1996

4. We refer to the sterilization validation studies of autoclave cycles.
 - a. The stoppers used at Fegersheim were received bagged and no further washing or preparation was indicated prior to sterilization. Are the stoppers certified or has the preparation of the stoppers been validated?
 - b. The sterilization validation studies for stoppers (both sites) used spores borne on paper strips rather than spores directly inoculated onto the stoppers. We acknowledge that the process lethality imparts a large overkill.
 - c. The stoppers sterilized in Indianapolis were contained in stainless steel cylinders. Please indicate whether thermocouples were used to probe the loaded cylinder. Did these demonstrate that air was not trapped in the cylinder and steam penetrated stoppers in the load? Were spore challenges located throughout the cylinder?
 - d. The sterilization of the filters for product solution was not addressed in biological challenge validation studies (both sites). Were the filters challenged as part of specific loads?
 - e. Please correct the Lilly equipment "Tag Number" for autoclave _____ Pages 16 and 25 (26 July 1995 amendment) identify this chamber with different "tag numbers".

5. We refer to the _____ studies for sterilization processes for vials.
 - a. The thermal specification for validation was _____ which is 25 to 100 fold less than the reported F_h values at Indianapolis. At Fegersheim the disparity was even greater. Therefore, this specification is not meaningful to the actual processes. For example, would a process with an F_h value of _____ reduce the endotoxin challenge by 3 logs?
 - b. The calculation of F_h was described as employing a D-value of _____ However, F-values are determined by integration of temperature using z-value and reference temperature. D-values are not a part of the equation F_T^z . Please explain the reference?

1 Page(s) Withheld

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

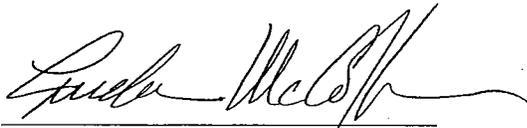
 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

March 27, 1996

9. Please confirm that the seals used for the container and closure system are sterilized by a validated process.
10. Please provide a time specification for storage of bulk unfiltered solution and for filtered product solution at the Fegersheim facility.
11. The process flow description for both sites fails to identify the stopper insertion and seating methods. Are these also part of the _____

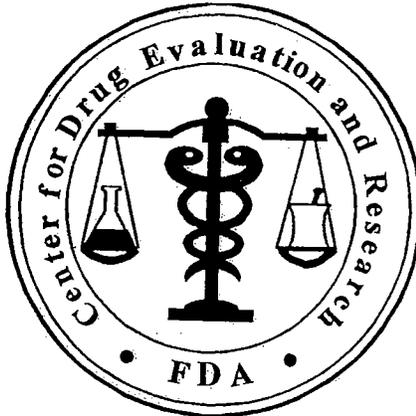
Should you have any questions, please contact Linda McCollum, CSO, at (301) 594-5771.



Linda McCollum, CSO
March 27, 1996

cc: Original NDA 20-509
HFD-150 Rev File
HFD-150/280 MCB

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

CDER, ODEI, Oncology (HFD-150), Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

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DATE: 27 Mar 96

PAGES SENT: 5 + COVER

TO: Kelly Freeman
Eli Lilly Res-Lab
Reg Affairs

FROM: LINDA McCOLLUM,
CSO, NDA 20-509
Stunz pr

PHONE: 317) 276-1337

PHONE: (301) 594-5771

FAX: 317) 276-1652

FAX: (301) 594-0498

COMMENTS:

TIME : MAR 27 '96 14:38
TEL NUMBER : 301-594-0498
NAME : FDA

NBR	FILE	DATE	TIME	DURATION	PGS	TO	DEPT NBR	MODE	STATUS
294	F.3	MAR.27	14:37	01/47	6	317 276 1652		EC	M OK

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

M E M O R A N D U M

DATE: November 1, 1994

FROM: Linda McCollum, CSO

SUBJECT: Minutes for Gemcitabine, Pancreatic Indication, Pre-NDA meeting
October 31, 1994.

TO: Dr. Kelly Freeman, Reg. Scientist, Eli Lilly & Co., No. Am. Reg. Affairs

FDA:

Dr. Robert Temple, Director, ODEI
Dr. Daniel Ihde, ODAC Member
Dr. Robert Justice, Group Leader, Oncology, DOPDP
Dr. Genevieve Schechter, Medical Reviewer
Dr. Mehul Mehta, Biopharmaceutics Supervisor
Dr. Lydia Kaus, Biopharmaceutics Reviewer
Dr. Clare Gnecco, Statistical Reviewer
Dr. Paul Dietze, Chemistry Reviewer
Ms. Linda McCollum, CSO

Sponsor:

Dr. Philip Reid, Vice President, US Medical Affiliate
Dr. Anna Maria Storniolo, Medical Director, Oncology
Dr. Peter Tarassoff, Physician
Dr. Robert Nelson, Physician
Dr. F. Andrew Dorr, Physician
Dr. John Andersen, Statistician
Dr. Clet Niyikiza, Statistician
Mr. Doug Schantz, Clinical Research Associate
Dr. Sandra Allerheiligen, Pharmacokineticist
Dr. Jeffrey Engelhardt, Toxicologist

*cc: Original NDA 20-589
HFD-150 / Div File
HFD-150 / CSO McCollum*

PRE-NDA MEETING MINUTES - OCTOBER 31, 1994

The meeting opened with introductions. Dr. Storniolo presented Lilly's agenda for discussion to resolve the following key questions:

1. After review of the pivotal trials, JHAY and JHAZ, of gemcitabine for pancreatic cancer, does the FDA feel that the data is sufficient to file an NDA?
2. Does the FDA feel that there is sufficient data to file an interim Treatment IND?
3. Can the NDA be given an expedited review?

Dr. John Andersen, Ph.D., statistician for Lilly Research Labs., presented an overview of results from the JHAY & JHAZ pivotal studies. In December, 1993 Lilly submitted a protocol to DOPDP which uses Clinical Benefit Response (CBR) as the primary endpoint. CBR would be measured by evaluation of performance status, analgesic consumption, and patient perception of pain using a set of definitions for improved, stable, or worsening response during a follow-up period of twelve weeks from initiation of treatment. Weight was classified as a secondary measure to be used when PS, analgesic consumption, and pain intensity were stable.

Objective response, survival, and time to progression were secondary endpoints. 5-FU was selected as the comparator drug since there is no clearly effective treatment for this condition.

Dr. Andersen presented slides showing the results of the clinical trial of Gemcitabine vs. 5-FU (JHAY) in untreated patients with pancreatic cancer and Gemcitabine alone in refractory patients (JHAZ) [see attached package] in terms of clinical benefit response. He mentioned that there were studies linking pain assessment and analgesic consumption to performance status singly but not together as is used in these studies. Lilly was trying to show a statistically significant direct relationship between CBR and performance status.

The data for the secondary endpoints indicated that the overall response in favor of Gemcitabine was 5% and that the median survival on the Gemcitabine arm in JHAY was 5.65 months, while on JHAZ median survival was 3.85 months. When asked by Dr. Temple why the results for the JHAZ study were so much worse, Dr. Andersen replied that all the patients on JHAZ had refractory cancer (had failed primary therapy with 5-FU). Time-to-Progression (TTP) was measured at 2.33 months for Gemcitabine vs. 0.92 month for 5-FU on JHAY and 2+ months on

JHAZ. Data for any patient who was removed from study was censored in these analyses. A third analysis of Time-to-Treatment Failure revealed for trial JHAY a TTF for Gemcitabine of 2.04 months vs. for 5-FU of 0.92 month. In JHAZ TTF was 2.07 months.

Analysis of clinical benefit response showed improved survival for the CBRers with a median survival for CBRs of 10.68 months vs. 4.77 months for non-CBRs. No analysis of clinical benefit response in terms of objective response has been performed.

Dr. Dorr reviewed the questions which Drs. Gnecco & Schechter had conveyed to the company October 25, 1994

1. With regard to question 1, the sponsor will provide individual patient profile listing as presented on pg.2 of their updated package, 9/29/94. These will be provided in tabular form with the weekly scores.
2. With regard to question 2, in addition to the 3 X 3 tables that the company provided as shown in the prepackage, breakdown of each of the patterns is needed. For each of the following combinations (Pain/KPS, Pain Intensity/ Analgesic Consumption, and Primary Measures of Clinical Benefit/Weight Change) a table of counts by arm should be provided. The company will provide this with the patients included in each table identified.
3. With regard to question 3, the company has agreed to plot the four individual components of CBR by medians over time. For the plots of median over time (weeks on study) for each component of CBR, Dr. Andersen suggested that there may be a potential bias in this type of display. Dr. Gnecco indicated that the data should still be graphed in this way to appreciate stability/change over time. During further discussion of this issue Dr. Schechter requested that graphs of each response group (complete and partial response, stable disease, and progression) in terms of CBR be provided. Dr. Temple suggested that the individual CBR parameters for each patient on each arm be graphed together in terms of response and that the graphs from each arm be juxtaposed to appreciate the differences in CBR between the two treatments. The patient IDs for patients included in each graph will be provided. In response to the company's question about the importance of this information in terms of the NDA submission Dr. Schechter stated that this information is very important in terms of review and that, in terms of priority, this analysis is in the upper half of the

priorities in terms of filing. Dr. Schechter explained that analysis of the CBR data in the way that the company proposed would be difficult.

Dr. Ihde commented that he also would like to see this data presented in graph form so that Agency/ODAC could scrutinize it carefully. When asked about the Treatment IND by Dr. Storniolo, Dr. Ihde said he has no strong feeling about it one way or the other.

4. With regard to question 4, the company will provide the plots of arm by median % change from baseline for each of the four components of CBR.
5. The company agrees to analyze by arm the time to achieve CBR and the duration of CBR.
6. The company will describe how the missing data is to be handled in the CBR analysis and at Dr. Gnecco's request will provide repeated measures analysis of covariance for individual components. The company expressed concern that such an analysis will bias the data.
7. The company agrees to do a thorough literature search to provide information about the survival and TTP in pancreatic cancer. The company asked if there were any prognostic factors which the Agency has identified for which analysis should be done. The Agency has not identified any factors. As requested, Cox proportional hazard models will be used to look at survival and TTP.
8. Which 3 studies do we want the tumor measurements for? The company and the FDA agree that there are two pivotal trials, B9E-MC-JHAY and B9E-MC-JHAZ. There are three supporting studies, B9E-MC-JHAL, B9E-MC-JHAL(ext), and B9E-EW-E012. The company was advised that the Phase II studies using the same dose schedule (B9E-MC-JHAL(ext) and B9E-EW-E012) should be included in the NDA. Dr. Temple agreed stating that, if these small studies contain survival data or TTP data, inclusion in the NDA was extremely important. Dr. Freeman asked that in order to facilitate the review would it be better to send in scanned images of the case reports for JHAL(ext) and E012. The printed case report forms do not have to be included as long as the electronic case report forms are available. Dr. Schechter said use of the electronic forms for these studies with paper

backup is okay. For the pivotal studies the printed case report forms will be included in the NDA.

Lilly will provide both early and late stage events logrank tests.

9. With regard to question 9, the company stated that the Mantel-Cox is the appropriate test to give more weight to later events. The company may also use other versions of the log-rank test to evaluate differences between weighting early and late events.
10. The company will provide information on the identity of those patients who had dose escalation with regard to time to progression and response.
11. The company will provide the identification of those patients who received growth factor, but stated few patients received GF because this drug is not myelosuppressive.
12. With regard to question 12, Lilly will provide JHAY safety data analyzed by grade of neutropenia, nadir counts and duration of neutropenia as requested for Gemcitabine.
13. The company will identify the number of patients who had grade III/IV anemia on each study as well as those patients who had thrombocytopenia.
14. The company was asked to identify those patients who had greater than grade I liver toxicity. The company was also asked to provide information about the correlation of liver toxicity with total dose and time on study.
15. With regard to the pulmonary toxicity experienced by some persons on Gemcitabine and to determine if the effect was due to drug or to disease, Dr. Schechter requested that the company categorize the patients who have dyspnea as a symptom with regard to other symptoms. Many of the patients with dyspnea are included in the pulmonary adverse reactions with more than one pulmonary adverse reaction, thus making it difficult to determine which patients may have a pulmonary toxicity due to Gemcitabine. Dr. Schechter will forward to the company an example giving an idea of how to arrange the information. A teleconference with the company will follow. The company was also asked to identify those patients who have flu-like symptoms and provide a list of these patients.

With regard to the Biopharm issues, Dr. Lydia Kaus asked about answers to the September 20, 1994 review comments. Lilly did not acknowledge receipt of these comments and the CSO will fax them a copy for review and comment. The company was asked whether any other metabolic pathways for this drug have been identified besides those reported to the IND. Dr. Allerheiligen answered that no other metabolic pathways have been reported. Thus far no explanation for the hepatic and pulmonary toxicities have been reported. Dr. Temple asked if there had been any correlation of AUC with dose and any correlation of AUC with clinical response at different dose levels. Dr. Temple expressed concern about the possibility of significant underdosing. Dr. Allerheiligen asked if the AUC would be looked at for CBR or toxicities. He answered, toxicities.

Dr. Storniolo concluded the meeting by recalling the three questions asked at the beginning of the meeting:

- 1) Is the data sufficient to file an NDA? For the information presented in the pre-meeting package the NDA appears to be fileable. The company indicated that the NDA would probably be filed in mid-January, 1995.
- 2) Since the data is acceptable for filing the NDA is it also acceptable to file a Treatment IND? It appears that a Treatment IND would be fileable. The timing of this filing will depend on the company.
- 3) Can the NDA be given an expedited review? Dr. Justice remarked that, as a matter of policy, all NDA reviews are expedited. Dr. Storniolo inquired if the Gemcitabine NDA would be presented at the 1st quarter ODAC meeting. Dr. Justice explained that the first 1995 ODAC meeting was scheduled for February and that this NDA review could not be completed in a four week time frame. The next ODAC meeting is tentatively scheduled for mid-June and that dates for the later meetings had not yet been set. At this time the FDA could not make a firm commitment as to the timing of an ODAC presentation.

The meeting concluded with these comments.



Lilly Research Laboratories

A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

February 1, 1995

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

Re: NDA 29-509--Gemzar® (gemcitabine hydrochloride)

This letter accompanies submission of an original New Drug Application (NDA) for Gemzar® (gemcitabine hydrochloride). Gemzar is a new intravenous oncolytic agent being submitted for the indication of pancreatic cancer. This application is formatted and organized according to 21 CFR § 314.50 and follows the "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications."

A pre-submission was made to this NDA on December 22, 1994 containing the chemistry, manufacturing and control data and the nonclinical pharmacology and toxicology data. This submission completes the initial NDA and provides the clinical, statistical, and pharmacokinetic data. A minor amendment to Item 3, the chemistry, manufacturing and control data, is also included. The initial User Fee due for this submission has already been paid; Form 3397 is provided.

The following summarizes the interactions and agreements reached with the Division of Oncology and Pulmonary Drug Products during the clinical investigations of gemcitabine under IND 29,653 as regards submission of an NDA for pancreatic cancer.

January 28, 1987

The initial IND (29,653) for gemcitabine was submitted.

January 24, 1992-
March 31, 1992

End-of-Phase 2 meeting and conference calls:

During these meetings, the protocol designs for the two studies to be used to fulfill the requirements to support registration in pancreatic cancer were developed with the advice and concurrence of the Division. Both trials were designed with clinical benefit response, a composite variable consisting of pain (pain intensity and analgesic consumption), performance status, and weight gain, as the primary endpoint. The first trial is a multi-center, single-blind, randomized, controlled study of gemcitabine versus with 5-Fluorouracil (5-FU) in previously untreated patients, Protocol B9E-MC-JHAY (JHAY). The second trial, Protocol B9E-MC-JHAZ (JHAZ), is a multi-center, single-arm study in 5-FU refractory patients. The final protocols were submitted to FDA on April 22, 1992.

Gemzar® (gemcitabine hydrochloride)
NDA 20-509

December 17, 1993

NDA formatting meeting:

During this meeting, several agreements were reached between Lilly and the FDA regarding the content of the NDA. It was agreed that full reports would be submitted for all pancreatic cancer studies while reports for all studies conducted in all other indications would be summaries or synopses. It was agreed that all clinical report forms (CRFs) would be provided for the pivotal studies, JHAY and JHAZ, and the notable patients (deaths, discontinuations due to adverse events, and serious, unexpected, possibly causally-related adverse events) from the other pancreatic cancer studies. For studies in all other indications, the Division agreed to accept patient summaries rather than CRFs, but retained the right to request additional CRFs during the review. Agreement was reached that the integrated safety analysis should be divided into three groups: A) studies at the recommended dose and schedule (all indications) B) the pancreatic cancer studies (a subset of A), and C) all other studies. The Division agreed that the Lilly database for reporting serious adverse events (DEN) would be appropriate to use for the data in the NDA from the data cut-off date to the date of submission and for the required safety updates. Information was also exchanged about the requirements for electronic submission of the statistical and pharmacokinetic analyses.

October 31, 1994

pre-NDA Meeting

Lilly presented the results of the pivotal trials, JHAY and JHAZ. The Division provided lists of recommended additional data presentations for both efficacy and safety. Lilly was asked to use the Cox proportional hazards models to explore prognostic factors. Requests for additional pharmacokinetic analyses were also received. Lilly was asked to provide all clinical report forms for the supporting pancreatic cancer studies, B9E-MC-JHAL, B9E-MC-JHAL (ext) and B9E-EW-E012, in addition to JHAY and JHAZ. Lilly suggested that all CRFs to be submitted be provided as CD-ROM electronic images. Following the meeting, it was agreed by teleconference this would be appropriate and that paper CRF copies would not be provided.

To coordinate our activities with yours, we suggest that any written communications, regardless of subject, concerning this application be directed to:

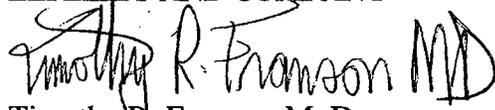
Dr. Timothy R. Franson
Executive Director
North American Regulatory Affairs
317-277-1324

Gemzar® (gemcitabine hydrochloride)
NDA 20-509

Please call Dr. Kelly Freeman at 317-276-1337 or me at 317-277-1324 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

Handwritten signature of Timothy R. Franson MD in black ink.

Timothy R. Franson, M. D.
Executive Director
North American Regulatory Affairs

TRF:ajf

Enclosures

cc: Ms. Linda McCollum (cover letter only)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-509

FEB 16 1995

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

Dear Dr. Franson:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Product: GEMZAR, gemcitabine hydrochloride, for Injection

Therapeutic Classification: P

Date of Application: February 1, 1995

Date of Receipt: February 2, 1995

Our Reference Number: NDA 20-509

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 3, 1995 in accordance with 21 CFR 314.101(b).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone

NDA 20-509

Page 2

report, or if you have any questions concerning this NDA, please contact:

Linda McCollum
Consumer Safety Officer
(301) 594-5771.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

D Pease 2-15-95

Dorothy Pease
Acting Chief, Project Management Staff
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

NDA 20-509
Page 3

cc:
Original NDA 20-509
HFD-150/Div. File
HFC-130
HFD-150/CSO-McCollum/rd 021095/021395

Initialed by: SCSO-Pease/021395 (Acting)

ACKNOWLEDGEMENT (AC)
doc. id. N20-509ak.feb

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

Form Approved: OMB No. 0910-0297
Expiration Date: November 30, 1996.

USER FEE COVER SHEET

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0297)
Washington, DC 20503

Please DO NOT RETURN this form to either of these addresses.

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

C/O Timothy R. Franson, M.D.
Executive Director
North American Regulatory Affairs

3. TELEPHONE NUMBER (Include Area Code)

(317) 277-1324

4. PRODUCT NAME

Gemzar (gemcitabine hydrochloride)

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

2726

7. LICENSE NUMBER/NDA NUMBER

NDA 20-509

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT
APPROVED BEFORE 9/1/92

THE APPLICATION IS SUBMITTED UNDER 505(b)(2)
(See reverse before checking box.)

AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 9/1/92

AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT
LICENSED UNDER 351 OF THE PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?

YES NO
(See reverse if answered YES)

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO
(See reverse if answered YES)

This completed form must be signed and accompany each new drug or biologic product, original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Timothy R. Franson MD

TITLE

Executive Director

DATE

2/1/95

**INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397**

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplement submitted to the Agency on or after January 1, 1994. The Prescription Drug User Fee Act of 1992, Public Law 102-571, authorizes the collection of the information requested on this form to implement the Act. Failure to complete this form may result in delay in processing of the submission.

ITEM NOS.

INSTRUCTIONS

1 - 3 Self-explanatory.

4 **PRODUCT NAME** - Include the generic name and the trade name, as applicable.

5 If clinical data are required for approval, then the application should be identified as containing clinical data. Please refer to the FDA policy regarding clinical data, Interim Guidance, Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under The Human Prescription Drug User Fee Act of 1992, July 12, 1993. Copies may be obtained from: Food and Drug Administration; Office of Small Business, Scientific and Trade Affairs; 5600 Fishers Lane, HF-50; Rockville, MD 20857. Please include two (2) pre-addressed mailing labels with your request.

6 **USER FEE I.D. NUMBER - PLEASE MAKE SURE THIS NUMBER AND THE NUMBER ON THE APPLICATION PAYMENT CHECK ARE THE SAME. FOR APPLICATIONS SUBJECT TO USER FEE PAYMENT**, please supply the following identifying information:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research Central Document Room, at (301) 443-8269.

FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the second characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 594-2906.

EXAMPLE: For U.S. License Number 4, product code ZZ01, with a document submission date of 8/3/93, the number would be: 0004ZZ0103AUG93.

7 **LICENSE NUMBER/NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

FOR DRUG PRODUCTS - Indicate the NDA number, if known, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 443-0035.

EXAMPLE: For NDA999999, the number would be: N0999999.

8 **EXCLUSIONS** - Check the appropriate box if this application is NOT covered by user fees because it is excluded from the definition of "human drug application" as defined in Section 735(1) and (2) of the Prescription Drug User Fee Act.

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or NOT a new indication for use.

9 **WAIVER** - Complete this section only if the application has qualified for the small business exception or a waiver has been granted for user fees for this application. A copy of the official FDA notification that the waiver has been granted must be provided with this submission.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-509

JAN 27 1995

Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Attention: M. W. Talbott, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Talbott:

We have received your presubmission of chemistry, manufacturing and controls, and pharmacology information for the following:

Name of Product: GEMZAR, gemcitabine hydrochloride, for Injection
Date of Application: December 22, 1994
Date of Receipt: December 23, 1994
Our Reference Number: NDA 20-509

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. If you have any questions regarding this information, please contact:

Linda McCollum
Consumer Safety Officer
(301) 594-5756

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

D. Pease 1-26-95
Dorothy Pease
Acting Chief, Project Management Staff
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

NDA 20-509
Page 2

cc:
Original NDA 20-509
HFD-150/Div. File
HFC-130
HFD-150/CSO-McCollum/rd 010395

Initialed by: SCSO

PRESUBMISSION ACKNOWLEDGEMENT (AC)
doc. id. N20-509ak.jan