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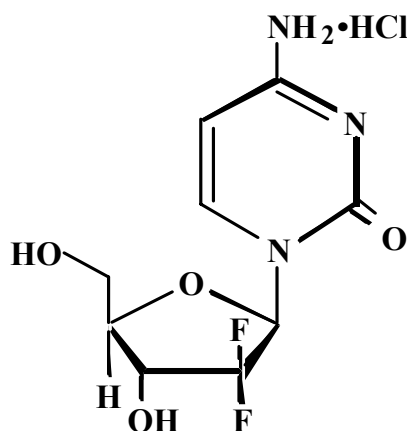
# GEMZAR<sup>®</sup> (GEMCITABINE HCl) FOR INJECTION

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## DESCRIPTION

6 Gemzar<sup>®</sup> (gemcitabine HCl) is a nucleoside analogue that exhibits antitumor activity.  
7 Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -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  
 37 effect 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/m<sup>2</sup>/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to  
 45 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the  
 46 inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the  
 47 excreted dose. The metabolite dFdU is also found in plasma. Gemcitabine plasma protein  
 48 binding is negligible.

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

54 Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model.  
 55 Population pharmacokinetic analyses of combined single and multiple dose studies showed that  
 56 the volume of distribution of gemcitabine was significantly influenced by duration of infusion  
 57 and gender. Clearance was affected by age and gender. Differences in either clearance or volume  
 58 of distribution based on patient characteristics or the duration of infusion result in changes in  
 59 half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine  
 60 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 Men (L/hr/m <sup>2</sup> )	Clearance Women (L/hr/m <sup>2</sup> )	Half-Life <sup>a</sup> Men (min)	Half-Life <sup>a</sup> 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

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

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64 Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long  
 65 infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly  
 66 increased volume of distribution with longer infusions. The lower clearance in women and the  
 67 elderly results in higher concentrations of gemcitabine for any given dose.

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

73 The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to  
 74 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without  
 75 undergoing further biotransformation. The metabolite did not accumulate with weekly dosing,

76 but its elimination is dependent on renal excretion, and could accumulate with decreased renal  
77 function.

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

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

83 *Drug Interactions* — When Gemzar (1250 mg/m<sup>2</sup> on Days 1 and 8) and cisplatin (75 mg/m<sup>2</sup> on  
84 Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was  
85 128 L/hr/m<sup>2</sup> and on Day 8 was 107 L/hr/m<sup>2</sup>. The clearance of cisplatin in the same study was  
86 reported to be 3.94 mL/min/m<sup>2</sup> with a corresponding half-life of 134 hours (*see Drug*  
87 *Interactions under PRECAUTIONS*). Analysis of data from metastatic breast cancer patients  
88 shows that, on average, Gemzar has little or no effect on the pharmacokinetics (clearance and  
89 half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of Gemzar.  
90 However, due to wide confidence intervals and small sample size, interpatient variability may be  
91 observed.

## 92 CLINICAL STUDIES

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

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

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**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 <sup>a</sup> ≥90	70.4%	74.4%	
Number of tumor sites			
1-2	56.6%	58.8%	
≥3	43.4%	41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	

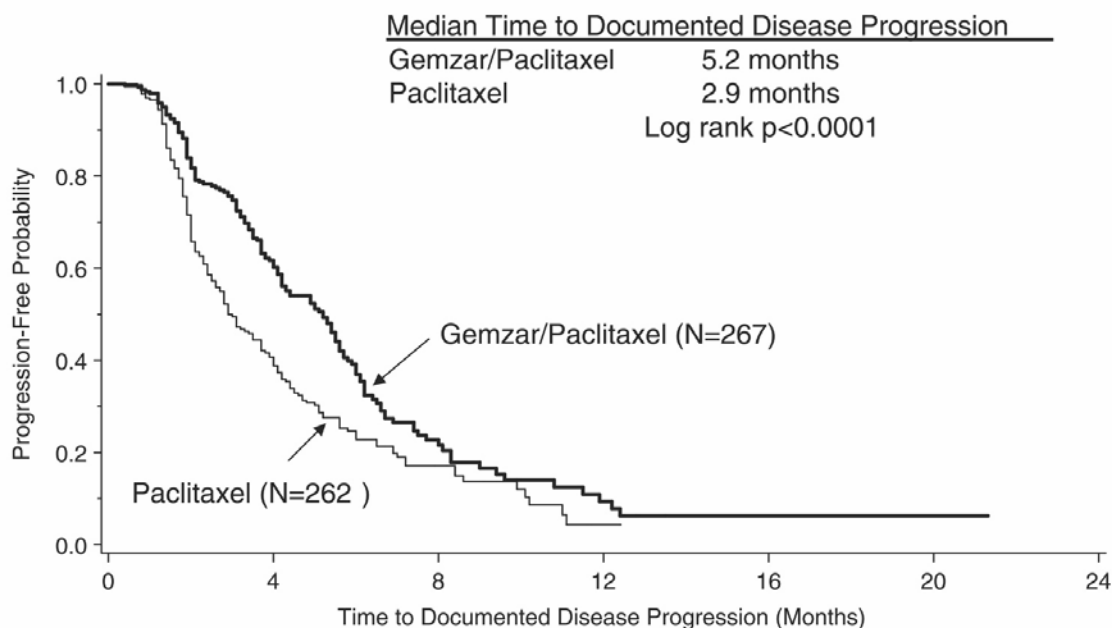
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Time to Documented Disease Progression <sup>b</sup>			p<0.0001
Median (95%, C.I.), months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)	
Hazard Ratio (95%, C.I.)	0.650 (0.524, 0.805)		p<0.0001
Overall Response Rate <sup>b</sup> (95%, C.I.)	40.8% (34.9, 46.7)	22.1%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

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

<sup>b</sup> These represent reconciliation of investigator and Independent Review Committee assessments according to a 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).**

114 *Non-Small Cell Lung Cancer (NSCLC)* — Data from 2 randomized clinical studies  
115 (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment  
116 of patients with locally advanced or metastatic NSCLC.

117 Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and  
118 Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received  
119 prior chemotherapy. Gemzar 1000 mg/m<sup>2</sup> was administered on Days 1, 8, and 15 of a 28-day  
120 cycle with cisplatin 100 mg/m<sup>2</sup> administered on Day 1 of each cycle. Single-agent cisplatin  
121 100 mg/m<sup>2</sup> was administered on Day 1 of each 28-day cycle. The primary endpoint was survival.  
122 Patient demographics are shown in Table 3. An imbalance with regard to histology was observed  
123 with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm  
124 having adenocarcinoma.

125 The Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the Gemzar  
126 plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm  
127 (Log rank p=0.008, two-sided). Median time to disease progression was 5.2 months on the

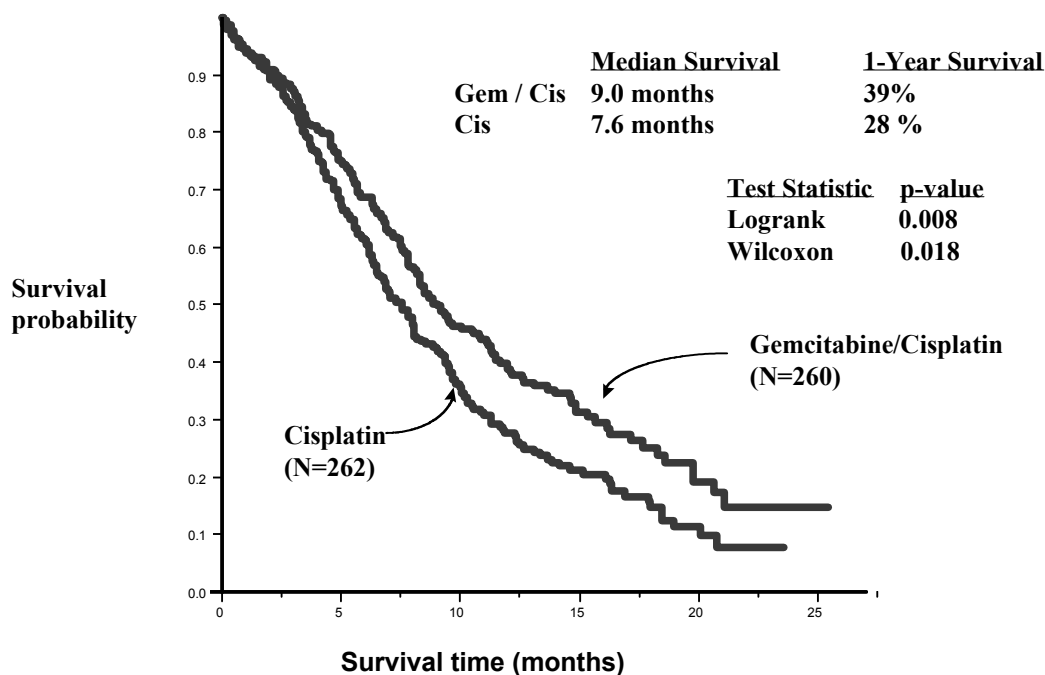
128 Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank  $p=0.009$ ,  
 129 two-sided). The objective response rate on the Gemzar plus cisplatin arm was 26% compared to  
 130 10% with cisplatin (Fisher's Exact  $p<0.0001$ , two-sided). No difference between treatment arms  
 131 with regard to duration of response was observed.

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

136 There was no significant difference in survival between the two treatment arms (Log rank  
 137  $p=0.18$ , two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm  
 138 versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for  
 139 the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus  
 140 cisplatin arm (Log rank  $p=0.015$ , two-sided). The objective response rate for the Gemzar plus  
 141 cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact  
 142  $p=0.01$ , two-sided).

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

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**Figure 2: Kaplan-Meier Survival Curve in Gemzar Plus Cisplatin Versus 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 <sup>a</sup>			21-day Schedule <sup>b</sup>		
	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 <sup>c</sup> 70 to 80	41%	44%		45%	52%	
Baseline KPS <sup>c</sup> 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 <sup>d</sup>	33%	14%	p=0.01 <sup>d</sup>

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

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<sup>b</sup> 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m<sup>2</sup> on Days 1 and 8 and cisplatin 100 mg/m<sup>2</sup> on Day 1

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every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 and I.V. etoposide 100 mg/m<sup>2</sup> on Days 1, 2, and 3 every 21 days.

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

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<sup>d</sup> 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 Log rank 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/m<sup>2</sup> over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

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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:

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179 i) the patient showed a  $\geq 50\%$  reduction in pain intensity (Memorial Pain Assessment Card)  
 180 or analgesic consumption, or a 20-point or greater improvement in performance status  
 181 (Karnofsky Performance Status) for a period of at least 4 consecutive weeks, without  
 182 showing any sustained worsening in any of the other parameters. Sustained worsening  
 183 was defined as 4 consecutive weeks with either any increase in pain intensity or analgesic  
 184 consumption or a 20-point decrease in performance status occurring during the first  
 185 12 weeks of therapy.

186 OR:

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

190 The first study was a multi-center (17 sites in US and Canada), prospective, single-blinded,  
 191 two-arm, randomized, comparison of Gemzar and 5-FU in patients with locally advanced or  
 192 metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was  
 193 administered intravenously at a weekly dose of  $600 \text{ mg/m}^2$  for 30 minutes. The results from this  
 194 randomized trial are shown in Table 4. Patients treated with Gemzar had statistically significant  
 195 increases in clinical benefit response, survival, and time to disease progression compared to  
 196 5-FU. The Kaplan-Meier curve for survival is shown in Figure 3. No confirmed objective tumor  
 197 responses were observed with either treatment.

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**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 <sup>a</sup> $\leq 70$	69.8%	68.3%	

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

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

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

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

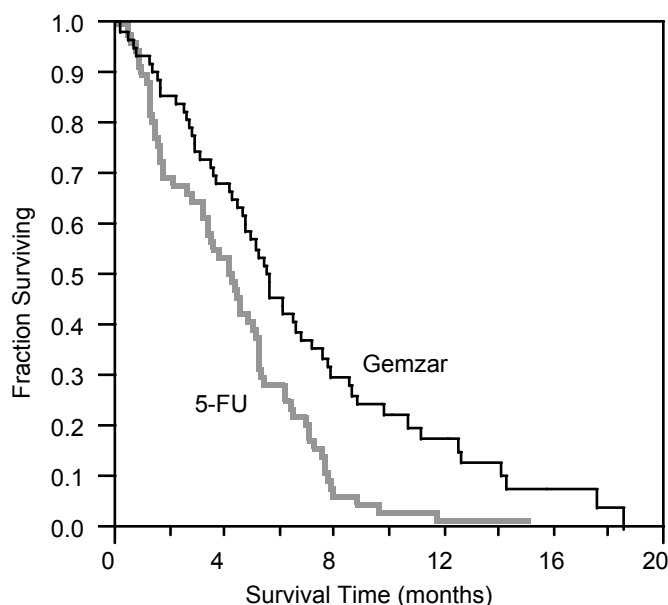
203 + No progression at last visit; remains alive.

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

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

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

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220 The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar  
221 in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a  
222 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median  
223 survival of 3.9 months.

224 *Other Clinical Studies* — When Gemzar was administered more frequently than once weekly  
225 or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase I  
226 study of Gemzar to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed  
227 that patients developed significant hypotension and severe flu-like symptoms that were  
228 intolerable at doses above 10 mg/m<sup>2</sup>. The incidence and severity of these events were  
229 dose-related. Other Phase I studies using a twice-weekly schedule reached MTDs of only  
230 65 mg/m<sup>2</sup> (30-minute infusion) and 150 mg/m<sup>2</sup> (5-minute bolus). The dose-limiting toxicities  
231 were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase I study to assess  
232 the maximum tolerated infusion time, clinically significant toxicity, defined as  
233 myelosuppression, was seen with weekly doses of 300 mg/m<sup>2</sup> at or above a 270-minute infusion  
234 time. The half-life of gemcitabine is influenced by the length of the infusion (*see CLINICAL*  
235 **PHARMACOLOGY**) and the toxicity appears to be increased if Gemzar is administered more  
236 frequently than once weekly or with infusions longer than 60 minutes (*see WARNINGS*).

## 237 INDICATIONS AND USAGE

### 238 Therapeutic Indications

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

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

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

## 248 CONTRAINDICATION

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

## 251 WARNINGS

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

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

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

262 *Renal* — Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported  
263 following one or more doses of Gemzar. Renal failure leading to death or requiring dialysis,  
264 despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal

265 failure leading to death were due to HUS (*see Renal under Single-Agent Use and under*  
 266 **Post-marketing experience in ADVERSE REACTIONS** section).

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

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

## 280 PRECAUTIONS

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

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

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

292 *Carcinogenesis, Mutagenesis, Impairment of Fertility* — Long-term animal studies to evaluate  
 293 the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward  
 294 mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo*  
 295 mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister  
 296 chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled  
 297 DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose  
 298 on a mg/m<sup>2</sup> basis) in male mice had an effect on fertility with moderate to severe  
 299 hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility  
 300 was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the  
 301 human dose on a mg/m<sup>2</sup> basis) and fetotoxicity or embryoletality was observed at  
 302 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m<sup>2</sup> basis).

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

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

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

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

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

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

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

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

### 332 **ADVERSE REACTIONS**

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

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

338 The data in Table 5 are based on 979 patients receiving Gemzar as a single-agent administered  
339 weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar  
340 starting doses ranged from 800 to 1250 mg/m<sup>2</sup>. Data are also shown for the subset of patients  
341 with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO  
342 Grade 3 or 4) adverse events were generally similar in the single-agent safety database of  
343 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the  
344 single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of  
345 patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse  
346 reactions was 14.3% for the Gemzar arm and 4.8% for the 5-FU arm.

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

353

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

	All Patients <sup>a</sup>			Pancreatic Cancer Patients <sup>b</sup>			Discontinuations (%) <sup>c</sup>
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
<b>Laboratory<sup>d</sup></b>							
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	
<b>Non-laboratory<sup>e</sup></b>							
Nausea and Vomiting	69	13	1	71	10	2	<1
Pain	48	9	<1	42	6	<1	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Constipation	23	1	<1	31	3	<1	0
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

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

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

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

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

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

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

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

	Gemzar <sup>a</sup>			5-FU <sup>b</sup>		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>c</sup></b>						
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
<b>Non-laboratory<sup>d</sup></b>						
Nausea and Vomiting	64	10	3	58	5	0
Pain	10	2	0	7	0	0
Fever	30	0	0	16	0	0
Rash	24	0	0	13	0	0
Dyspnea	6	0	0	3	0	0
Constipation	10	3	0	11	2	0
Diarrhea	24	2	0	31	5	0
Hemorrhage	0	0	0	2	0	0
Infection	8	0	0	3	2	0
Alopecia	18	0	0	16	0	0
Stomatitis	14	0	0	15	0	0
Somnolence	5	2	0	7	2	0
Paresthesias	2	0	0	2	0	0

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

363 <sup>a</sup> N=58-63; all Gemzar patients with laboratory or non-laboratory data.

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

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

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

367

368 *Hematologic* — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity  
369 with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or  
370 thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence  
371 of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was  
372 reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients

373 should be monitored for myelosuppression during Gemzar therapy and dosage modified or  
374 suspended according to the degree of hematologic toxicity (*see* **DOSAGE AND**  
375 **ADMINISTRATION**).

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

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

385 *Renal* — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical  
386 findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of  
387 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on  
388 Gemzar therapy, 2 immediately post-therapy. The diagnosis of HUS should be considered if the  
389 patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or  
390 LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of  
391 serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure  
392 may not be reversible even with discontinuation of therapy and dialysis may be required (*see*  
393 *Renal under Post-marketing experience*).

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

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

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

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

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

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

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

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

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

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

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

427 **Combination Use in Non-Small Cell Lung Cancer:** In the Gemzar plus cisplatin versus  
428 cisplatin study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin  
429 injections on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were  
430 required in greater than 90% of patients on the combination, versus 16% on cisplatin. Study  
431 discontinuations for possibly drug-related adverse events occurred in 15% of patients on the  
432 combination arm and 8% of patients on the cisplatin arm. With a median of 4 cycles of Gemzar  
433 plus cisplatin treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due  
434 to possibly treatment-related adverse events. With a median of 2 cycles of cisplatin treatment,  
435 61 of 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related  
436 adverse events.

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

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

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

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

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

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

478 Table 8 presents data from the randomized study of Gemzar plus cisplatin versus etoposide  
 479 plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in  
 480 Table 6. One death (1.5%) was reported on the Gemzar plus cisplatin arm due to febrile  
 481 neutropenia associated with renal failure which was possibly treatment-related. No deaths related  
 482 to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4  
 483 neutropenia on the Gemzar plus cisplatin arm was less than on the etoposide plus cisplatin  
 484 arm (28% versus 56%). Sepsis was experienced by 2% of patients on both treatment arms.  
 485 Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the Gemzar plus  
 486 cisplatin arm. RBC transfusions were given to 29% of the patients who received Gemzar plus  
 487 cisplatin versus 21% of patients who received etoposide plus cisplatin. Platelet transfusions were  
 488 given to 3% of the patients who received Gemzar plus cisplatin versus 8% of patients who  
 489 received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the  
 490 Gemzar plus cisplatin arm. On the Gemzar plus cisplatin arm, 7% of participants were  
 491 hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm.  
 492 More than twice as many patients had dose reductions or omissions of a scheduled dose of  
 493 Gemzar as compared to etoposide, which may explain the differences in the incidence of  
 494 neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by  
 495 3% of patients on the Gemzar plus cisplatin arm with none reported on the comparator arm.  
 496 Eight patients (12%) on the Gemzar plus cisplatin arm reported edema compared to  
 497 one patient (2%) on the etoposide plus cisplatin arm.  
 498

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

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

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

503 <sup>b</sup> N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m<sup>2</sup> on Day 1 every  
504 28 days.

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

506 <sup>d</sup> Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

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

508

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

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

510 <sup>a</sup> N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m<sup>2</sup> on  
511 Days 1 and 8 and cisplatin at 100 mg/m<sup>2</sup> on Day 1 every 21 days.

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

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

515 <sup>d</sup> Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.

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

517 <sup>f</sup> Pain data were not collected.

518

519 **Combination Use in Breast Cancer:** In the Gemzar plus paclitaxel versus paclitaxel study,  
 520 dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the  
 521 combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar  
 522 doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel  
 523 doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemzar plus paclitaxel arm and  
 524 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were  
 525 two deaths on study or within 30 days after study drug discontinuation that were possibly  
 526 drug-related, one on each arm.

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

529

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

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

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

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

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

533

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

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

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

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

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

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

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

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

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

565

## OVERDOSAGE

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

571

## DOSAGE AND ADMINISTRATION

572 *Gemzar is for intravenous use only.*

### Adults

#### Single-Agent Use:

575 *Pancreatic Cancer* — Gemzar should be administered by intravenous infusion at a dose of  
576  $1000 \text{ mg/m}^2$  over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates

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

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

583 Patients receiving Gemzar should be monitored prior to each dose with a complete blood  
584 count (CBC), including differential and platelet count. If marrow suppression is detected,  
585 therapy should be modified or suspended according to the guidelines in Table 10.  
586

**Table 10: Dosage Reduction Guidelines**

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

587  
588 Laboratory evaluation of renal and hepatic function, including transaminases and serum  
589 creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemzar  
590 should be administered with caution in patients with evidence of significant renal or hepatic  
591 impairment.

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

#### 599 **Combination Use:**

600 *Non-Small Cell Lung Cancer* — Two schedules have been investigated and the optimum  
601 schedule has not been determined (*see CLINICAL STUDIES*). With the 4-week schedule,  
602 Gemzar should be administered intravenously at 1000 mg/m<sup>2</sup> over 30 minutes on Days 1, 8, and  
603 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m<sup>2</sup> on Day 1  
604 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered  
605 intravenously at 1250 mg/m<sup>2</sup> over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at  
606 a dose of 100 mg/m<sup>2</sup> should be administered intravenously after the infusion of Gemzar on  
607 Day 1. See prescribing information for cisplatin administration and hydration guidelines.

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

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

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

621 *Breast Cancer* — Gemzar should be administered intravenously at a dose of 1250 mg/m<sup>2</sup> over  
622 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at  
623 175 mg/m<sup>2</sup> on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients  
624 should be monitored prior to each dose with a complete blood count, including differential  
625 counts. Patients should have an absolute granulocyte count  $\geq 1500 \times 10^6/L$  and a platelet count  
626  $\geq 100,000 \times 10^6/L$  prior to each cycle.

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

630

**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
$\geq 1200$	and	$>75,000$	100
1000-1199	or	50,000-75,000	75
700-999	and	$\geq 50,000$	50
$<700$	or	$<50,000$	Hold

631

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

636 Gemzar may be administered on an outpatient basis.

637 *Instructions for Use/Handling* — The recommended diluent for reconstitution of Gemzar is  
638 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the  
639 maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at  
640 concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be  
641 avoided.

642 To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of  
643 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a  
644 gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume  
645 of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total  
646 volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of  
647 the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate  
648 amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride  
649 Injection to concentrations as low as 0.1 mg/mL.

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

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

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

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

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

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

671

## HOW SUPPLIED

### Vials:

673 200 mg white, lyophilized powder in a 10-mL size sterile single use vial (No. 7501)

674 NDC 0002-7501-01

675 1 g white, lyophilized powder in a 50-mL size sterile single use vial (No. 7502)

676 NDC 0002-7502-01

677

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

684

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