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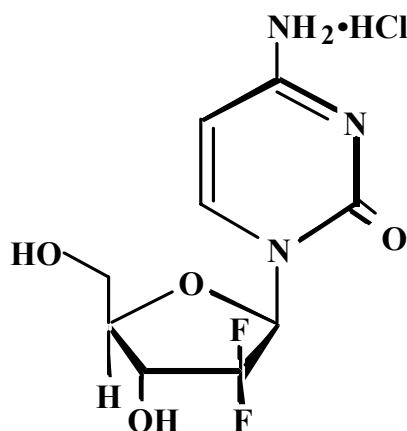
GEMZAR[®] (GEMCITABINE HCl) FOR INJECTION

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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
 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/m²/30 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/m².

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

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

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64 Gemcitabine half-life for short infusions ranged from 32 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/m² 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/m², 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/m² on Days 1 and 8) and cisplatin (75 mg/m² on
84 Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was
85 128 L/hr/m² and on Day 8 was 107 L/hr/m². The clearance of cisplatin in the same study was
86 reported to be 3.94 mL/min/m² with a corresponding half-life of 134 hours (*see Drug*
87 *Interactions under PRECAUTIONS*).

88 CLINICAL STUDIES

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

95 The addition of Gemzar to paclitaxel resulted in statistically significant improvement in time to
96 documented disease progression and overall response rate compared to monotherapy with
97 paclitaxel as shown in Table 2 and Figure 1. Further, there was a strong trend toward improved
98 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

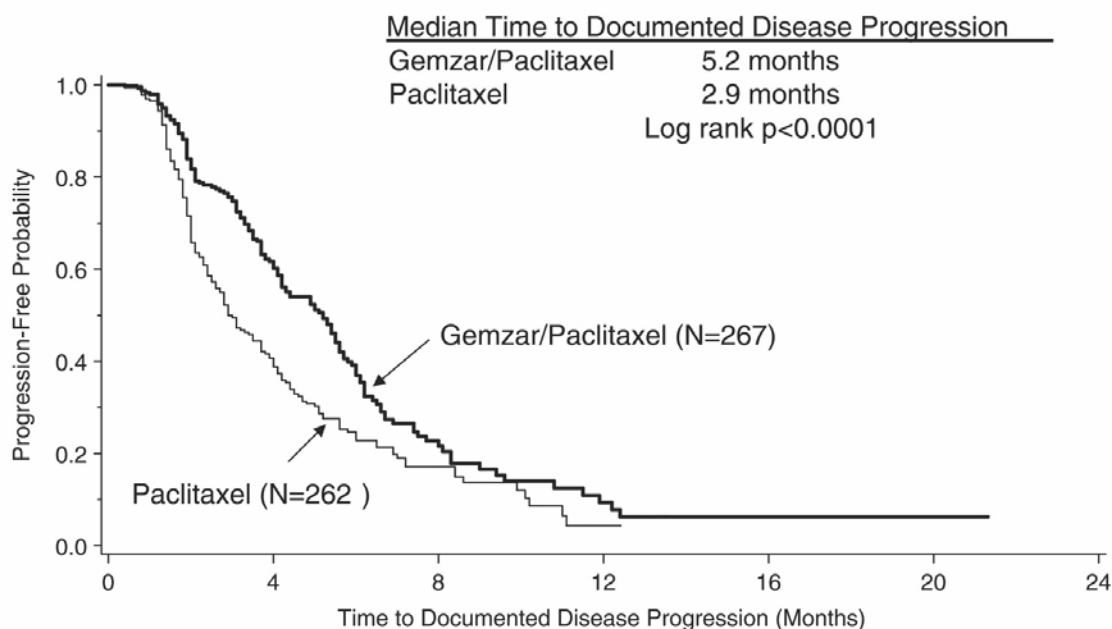
	Gemzar/Paclitaxel	Paclitaxel	
Number of patients	267	262	
Median age, years	53	52	
Range	26 to 83	26 to 75	
Metastatic disease	97.0%	96.9%	
Baseline KPS ^a ≥90	70.4%	74.4%	
Number of tumor sites			
1-2	56.6%	58.8%	
≥3	43.4%	41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	
Time to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

^a Karnofsky Performance Status.

^b 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).

109 *Non-Small Cell Lung Cancer (NSCLC)* — Data from 2 randomized clinical studies
110 (657 patients) support the use of Gemzar in combination with cisplatin for the first-line treatment
111 of patients with locally advanced or metastatic NSCLC.

112 Gemzar plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and
113 Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received
114 prior chemotherapy. Gemzar 1000 mg/m² was administered on Days 1, 8, and 15 of a 28-day
115 cycle with cisplatin 100 mg/m² administered on Day 1 of each cycle. Single-agent cisplatin
116 100 mg/m² was administered on Day 1 of each 28-day cycle. The primary endpoint was survival.
117 Patient demographics are shown in Table 3. An imbalance with regard to histology was observed
118 with 48% of patients on the cisplatin arm and 37% of patients on the Gemzar plus cisplatin arm
119 having adenocarcinoma.

120 The Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the Gemzar
121 plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm
122 (Logrank $p=0.008$, two-sided). Median time to disease progression was 5.2 months on the
123 Gemzar plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank $p=0.009$,
124 two-sided). The objective response rate on the Gemzar plus cisplatin arm was 26% compared to
125 10% with cisplatin (Fisher's Exact $p<0.0001$, two-sided). No difference between treatment arms
126 with regard to duration of response was observed.

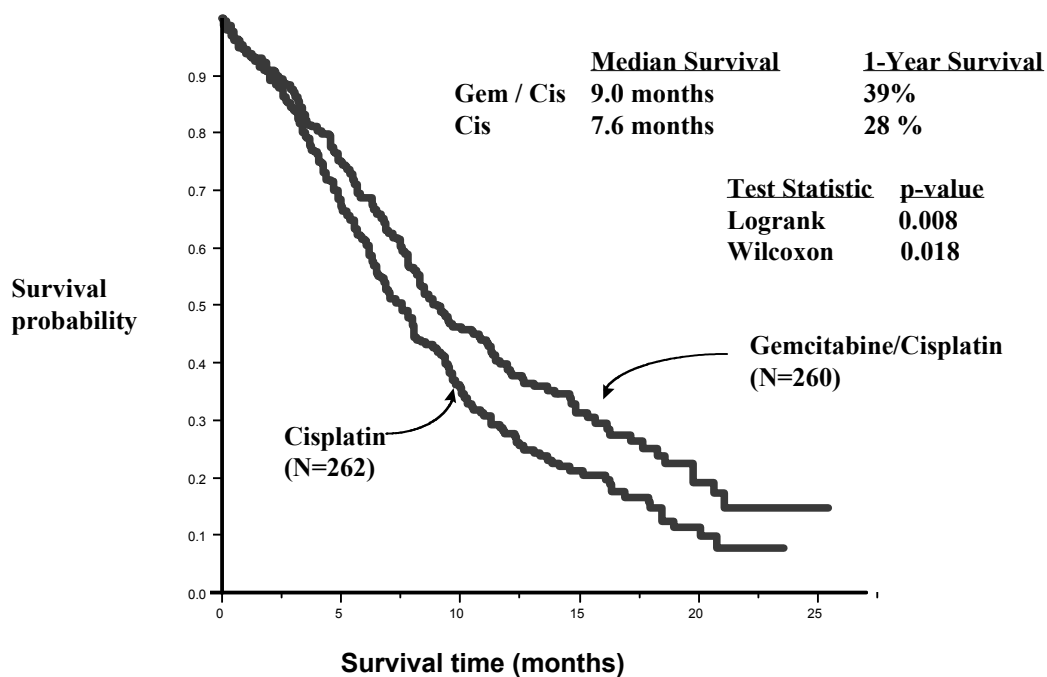
127 Gemzar plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in
128 Stage IIIB or IV NSCLC randomized 135 patients to Gemzar 1250 mg/m² on Days 1 and 8, and
129 cisplatin 100 mg/m² on Day 1 of a 21-day cycle or to etoposide 100 mg/m² I.V. on Days 1, 2,
130 and 3 and cisplatin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

131 There was no significant difference in survival between the two treatment arms (Logrank
132 $p=0.18$, two-sided). The median survival was 8.7 months for the Gemzar plus cisplatin arm

133 versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for
 134 the Gemzar plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus
 135 cisplatin arm (Logrank $p=0.015$, two-sided). The objective response rate for the Gemzar plus
 136 cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact
 137 $p=0.01$, two-sided).

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

149 ^a 28-day schedule — Gemzar plus cisplatin: Gemzar 1000 mg/m² on Days 1, 8, and 15 and cisplatin 100 mg/m² on

150 Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m² on Day 1 every 28 days.

151 ^b 21-day schedule — Gemzar plus cisplatin: Gemzar 1250 mg/m² on Days 1 and 8 and cisplatin 100 mg/m² on

152 Day 1

153 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m² on Day 1 and I.V. etoposide

154 100 mg/m² on Days 1, 2, and 3 every 21 days.

155 ^c Karnofsky Performance Status.

156 ^d p-value for tumor response was calculated using the two-sided Fisher's exact test for difference in binomial

157 proportions. All other p-values were calculated using the Logrank test for difference in overall time to an event.

158 N/A Not applicable.

159

160 *Pancreatic Cancer* — Data from 2 clinical trials evaluated the use of Gemzar in patients with

161 locally advanced or metastatic pancreatic cancer. The first trial compared Gemzar to

162 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial

163 studied the use of Gemzar in pancreatic cancer patients previously treated with 5-FU or a

164 5-FU-containing regimen. In both studies, the first cycle of Gemzar was administered

165 intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until

166 toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemzar.

167 Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every

168 4 weeks.

169 The primary efficacy parameter in these studies was “clinical benefit response,” which is a

170 measure of clinical improvement based on analgesic consumption, pain intensity, performance

171 status, and weight change. Definitions for improvement in these variables were formulated

172 prospectively during the design of the 2 trials. A patient was considered a clinical benefit

173 responder if either:

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

181 OR:

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

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

193

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%	

194

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	

195 ^a Karnofsky Performance Status.

196 ^b Kaplan-Meier estimates.

197 ^c N=number of patients.

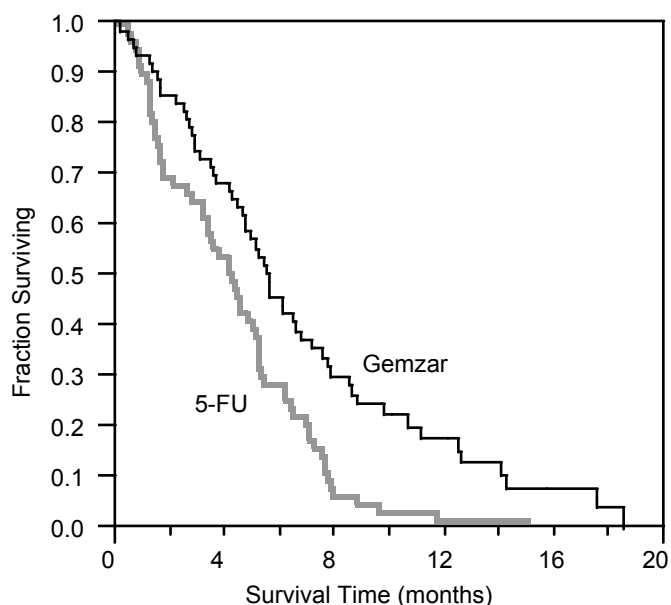
198 + No progression at last visit; remains alive.

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

201

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

211



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Figure 3: Kaplan-Meier Survival Curve.

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215 The second trial was a multi-center (17 US and Canadian centers), open-label study of Gemzar
216 in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a
217 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median
218 survival of 3.9 months.

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

232 INDICATIONS AND USAGE

233 Therapeutic Indications

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

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

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

243 CONTRAINDICATION

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

246 WARNINGS

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

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

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

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

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

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

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

275 **PRECAUTIONS**

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

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

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

287 *Carcinogenesis, Mutagenesis, Impairment of Fertility* — Long-term animal studies to evaluate
288 the carcinogenic potential of Gemzar have not been conducted. Gemcitabine induced forward
289 mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo*
290 mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister
291 chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled
292 DNA synthesis *in vitro*. Gemcitabine I.P. doses of 0.5 mg/kg/day (about 1/700 the human dose
293 on a mg/m² basis) in male mice had an effect on fertility with moderate to severe
294 hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility
295 was not affected but maternal toxicities were observed at 1.5 mg/kg/day I.V. (about 1/200 the
296 human dose on a mg/m² basis) and fetotoxicity or embryoletality was observed at
297 0.25 mg/kg/day I.V. (about 1/1300 the human dose on a mg/m² basis).

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

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

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

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

317 *Pediatric Patients* — The effectiveness of Gemzar in pediatric patients has not been
318 demonstrated. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory
319 leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes
320 three times weekly followed by a one week rest period. Gemzar was also evaluated in a Phase 2
321 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous
322 leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a
323 one week rest period. Toxicities observed included bone marrow suppression, febrile
324 neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were
325 similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2
326 trial.

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

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

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

335 **ADVERSE REACTIONS**

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

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

341 The data in Table 5 are based on 979 patients receiving Gemzar as a single-agent administered
342 weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemzar
343 starting doses ranged from 800 to 1250 mg/m². Data are also shown for the subset of patients
344 with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO
345 Grade 3 or 4) adverse events were generally similar in the single-agent safety database of
346 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the
347 single-agent safety database resulted in discontinuation of Gemzar therapy in about 10% of
348 patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse
349 reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm.

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

356

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

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

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

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

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

^c N=979.

^d Regardless of causality.

^e Table includes non-laboratory data with incidence for all patients $\geq 10\%$. 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 ^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

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

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

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

368 ^c Regardless of causality.

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

370

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

430 **Combination Use in Non-Small Cell Lung Cancer:** In the Gemzar plus cisplatin vs. cisplatin
431 study, dose adjustments occurred with 35% of Gemzar injections and 17% of cisplatin injections
432 on the combination arm, versus 6% on the cisplatin-only arm. Dose adjustments were required in
433 greater than 90% of patients on the combination, versus 16% on cisplatin. Study discontinuations
434 for possibly drug-related adverse events occurred in 15% of patients on the combination arm and
435 8% of patients on the cisplatin arm. With a median of 4 cycles of Gemzar plus cisplatin
436 treatment, 94 of 262 patients (36%) experienced a total of 149 hospitalizations due to possibly
437 treatment-related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of
438 260 patients (23%) experienced 78 hospitalizations due to possibly treatment-related adverse
439 events.

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

455 Table 7 presents the safety data from the Gemzar plus cisplatin vs. cisplatin study in non-small
456 cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug
457 combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths,
458 including 3 resulting from myelosuppression with infection and 1 case of renal failure associated
459 with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm.
460 Nine cases of febrile neutropenia were reported on the combination therapy arm compared to
461 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the Gemzar plus
462 cisplatin arm.

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

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

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

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

481 Table 8 presents data from the randomized study of Gemzar plus cisplatin versus etoposide
 482 plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in
 483 Table 6. One death (1.5%) was reported on the Gemzar plus cisplatin arm due to febrile
 484 neutropenia associated with renal failure which was possibly treatment-related. No deaths related
 485 to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4
 486 neutropenia on the Gemzar plus cisplatin arm was less than on the etoposide plus cisplatin
 487 arm (28% vs. 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3
 488 anemia and Grade 3/4 thrombocytopenia were more common on the Gemzar plus cisplatin arm.
 489 RBC transfusions were given to 29% of the patients who received Gemzar plus cisplatin vs. 21%
 490 of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the
 491 patients who received Gemzar plus cisplatin vs. 8% of patients who received etoposide plus
 492 cisplatin. Grade 3/4 nausea and vomiting were also more common on the Gemzar plus cisplatin
 493 arm. On the Gemzar plus cisplatin arm, 7% of participants were hospitalized due to febrile
 494 neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many
 495 patients had dose reductions or omissions of a scheduled dose of Gemzar as compared to
 496 etoposide, which may explain the differences in the incidence of neutropenia and febrile
 497 neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the
 498 Gemzar plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on
 499 the Gemzar plus cisplatin arm reported edema compared to 1 patient (2%) on the etoposide plus
 500 cisplatin arm.
 501

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

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

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

506 ^b N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 every
507 28 days.

508 ^c Regardless of causality.

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

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

511

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

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

513 ^a N=67-69; all Gemzar plus cisplatin patients with laboratory or non-laboratory data. Gemzar at 1250 mg/m² on
514 Days 1 and 8 and cisplatin at 100 mg/m² on Day 1 every 21 days.

515 ^b N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on
516 Day 1 and I.V. etoposide at 100 mg/m² on Days 1, 2, and 3 every 21 days.

517 ^c Regardless of causality.

518 ^d Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events.

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

520 ^f Pain data were not collected.

521

522 **Combination Use in Breast Cancer:** In the Gemzar plus paclitaxel versus paclitaxel study,
 523 dose reductions occurred with 8% of Gemzar injections and 5% of paclitaxel injections on the
 524 combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemzar
 525 doses were omitted and <1% of paclitaxel doses were omitted, compared to <1% of paclitaxel
 526 doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemzar plus paclitaxel arm and
 527 12 (5%) on the paclitaxel arm discontinued the study because of adverse events. There were
 528 two deaths on study or within 30 days after study drug discontinuation that were possibly
 529 drug-related, one on each arm.

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

532

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

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

534 ^b Regardless of causality.

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

536

537 The following are the clinically relevant adverse events that occurred in $>1\%$ and $<10\%$ (all
538 grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse
539 events (Gemzar plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%),
540 infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity
541 (0 versus 0.8%).

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

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

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

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

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

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

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

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

568

OVERDOSAGE

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

574

DOSAGE AND ADMINISTRATION

575 *Gemzar is for intravenous use only.*

Adults

Single-Agent Use:

578 *Pancreatic Cancer* — Gemzar should be administered by intravenous infusion at a dose of
579 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates

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

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

586 Patients receiving Gemzar should be monitored prior to each dose with a complete blood
587 count (CBC), including differential and platelet count. If marrow suppression is detected,
588 therapy should be modified or suspended according to the guidelines in Table 10.
589

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

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

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

602 **Combination Use:**

603 *Non-Small Cell Lung Cancer* — Two schedules have been investigated and the optimum
604 schedule has not been determined (*see CLINICAL STUDIES*). With the 4-week schedule,
605 Gemzar should be administered intravenously at 1000 mg/m² over 30 minutes on Days 1, 8, and
606 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m² on Day 1
607 after the infusion of Gemzar. With the 3-week schedule, Gemzar should be administered
608 intravenously at 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at
609 a dose of 100 mg/m² should be administered intravenously after the infusion of Gemzar on
610 Day 1. See prescribing information for cisplatin administration and hydration guidelines.

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

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

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

624 *Breast Cancer* — Gemzar should be administered intravenously at a dose of 1250 mg/m² over
625 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at
626 175 mg/m² on Day 1 as a 3-hour intravenous infusion before Gemzar administration. Patients
627 should be monitored prior to each dose with a complete blood count, including differential
628 counts. Patients should have an absolute granulocyte count $\geq 1500 \times 10^6/L$ and a platelet count
629 $\geq 100,000 \times 10^6/L$ prior to each cycle.

630 *Dose Modifications* — Gemzar dosage adjustments for hematological toxicity is based on the
631 granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected,
632 Gemzar dosage should be modified according to the guidelines in Table 11.
633

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

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

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

639 Gemzar may be administered on an outpatient basis.

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

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

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

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

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

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

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

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

674 HOW SUPPLIED

675 Vials:

676 200 mg white, lyophilized powder in a 10-mL size sterile single use vial (No. 7501)

677 NDC 0002-7501-01

678 1 g white, lyophilized powder in a 50-mL size sterile single use vial (No. 7502)

679 NDC 0002-7502-01

680

681 Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined
682 controlled room temperature as “A temperature maintained thermostatically that encompasses
683 the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a
684 mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions
685 between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and
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709 **Indianapolis, IN 46285, USA**

710 B1.0 NL 4063 AMP

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