

# Gemita - Pack Insert

For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

## GEMCITABINE

### GEMITA

Lyophilized Powder for Injection (IV Infusion)

#### DESCRIPTION:

Gemcitabine HCl is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. Gemcitabine for Injection is a white to off white lyophilized powder or cake.

#### Formulation:

<b>Gemcitabine (Gemita) 200 mg</b>	
Each vial contains:	
Gemcitabine Hydrochloride	200 mg
Equivalent to Gemcitabine	200 mg
Mannitol	12.5mg
Sodium acetate	to adjust pH
Hydrochloric acid and/or Sodium hydroxide	

#### Gemcitabine (Gemita) 1g

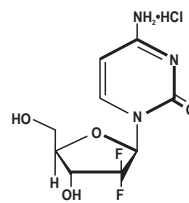
Each vial contains:	
Gemcitabine Hydrochloride	1 g
Equivalent to Gemcitabine	1 g
Mannitol	62.5mg
Sodium acetate	to adjust pH
Hydrochloric acid and/or Sodium hydroxide	

#### Gemcitabine (Gemita) 1.4g

Each vial contains:	
Gemcitabine Hydrochloride	1.4 g
Equivalent to Gemcitabine	1.4 g
Mannitol	87.5mg
Sodium acetate	to adjust pH
Hydrochloric acid and/or Sodium hydroxide	

#### CHEMICAL STRUCTURE:

The chemical name for Gemcitabine HCl is 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is C<sub>8</sub>H<sub>9</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>·HCl. It has a molecular weight of 299.66. The formulation is supplied in a sterile form for intravenous use only. Vials contain 200 mg, 1 g or 1.4 g of gemcitabine HCl (expressed as free base) as a sterile lyophilized powder. The structural formula of gemcitabine is depicted below.



#### CLINICAL PHARMACOLOGY:

##### Mechanism of action

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

##### Pharmacokinetics

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

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

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

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

Age	Clearance Men (L/hr/m <sup>2</sup> )	Clearance Women (L/hr/m <sup>2</sup> )	Half-life Men (min)	Half-life 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

\*Half-life for patients receiving a short infusion (<70 min)

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

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m<sup>2</sup> following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long

infusions, the volume of distribution rose to 370 L/ m<sup>2</sup>, reflecting slow equilibration of gemcitabine within the tissue compartment.

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

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

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

#### CLINICAL STUDIES:

##### Ovarian Cancer:

Gemcitabine was studied in a randomized Phase 3 study of 356 patients with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either Gemcitabine 1000 mg/ m<sup>2</sup> on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemcitabine on Day 1 of each cycle or single-agent carboplatin AUC 5 administered on Day 1 of each 21-day cycle as the control arm. The primary endpoint of this study was progression free survival (PFS).

Patient characteristics are shown in Table 2. The addition of Gemcitabine to carboplatin resulted in statistically significant improvement in PFS and overall response rate as shown in Table 3. Approximately 75% of patients in each arm received poststudy chemotherapy. Only 13 of 120 patients with documented poststudy chemotherapy regimen in the carboplatin arm received Gemcitabine after progression. There was not a significant difference in overall survival between arms.

Table 2: Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Baseline Demographics and Clinical Characteristics

	Gemcitabine/Carboplatin	Carboplatin
Number of randomized patients	178	178
Median age, years, Range	59 36 to 78	58 21-81
Baseline ECOG performance status 0-1*	94%	95%
Disease Status		
Evaluate	7.9%	2.8%
Bidimensionally measurable	91.6%	95.5%
Platinum-free interval <sup>†</sup>		
6-12 month	39.9%	39.9%
>12 month	59.0%	59.6%
First-line therapy		
Platinum-taxane combination	70.2%	71.3%
Platinum-non-taxane combination	28.7%	27.5%
Platinum monotherapy	1.1%	1.1%

\*Nine patients (5 on the Gemcitabine plus carboplatin arm and 4 on the carboplatin arm) did not have baseline Eastern Cooperative Oncology Group (ECOG) performance status recorded.

<sup>†</sup>Three patients (2 on the Gemcitabine plus carboplatin arm and 1 on the carboplatin arm) had a platinum-free interval of less than 6 months.

Table 3: Gemcitabine Plus Carboplatin versus Carboplatin in Ovarian Cancer - Results of Efficacy Analysis

	Gemcitabine/ Carboplatin (N=178)	Carboplatin (N=178)	
PFS	8.6(8.0,9.7)	5.8(5.2,7.1)	P=0.0038*
Median (95%, C.I.) months			
Hazard Ratio (95%, C.I.)	0.72(0.57, 0.90)		
Overall Survival	18.0(16.2,20.3)	17.3(15.2,19.3)	P=0.8977*
Median(95%,C.I.) months	0.98(0.78,1.24)		
Hazard Ratio (95%, C.I.)	0.86(0.67,1.10)		
Adjusted Hazard Ratio(95%,C.I.)			
Investigator Reviewed			
Overall Response Rate	47.2	30.9	P=0.0016*
CR	14.6	6.2	
PR+PRNM <sup>‡</sup>	32.6	24.7	
Independently Reviewed			
Overall Response Rate <sup>‡</sup>	46.3%	35.6%	P=0.11*
CR	9.1%	4.0%	
PR+PRNM	37.2%	31.7%	

\*Treatment adjusted for performance status, tumor area, and platinum-free interval.

<sup>†</sup>Partial response non-measurable disease

<sup>‡</sup>Independent reviewers could not evaluate disease demonstrated by sonography or physical exam.

<sup>§</sup>Log Rank, unadjusted

<sup>¶</sup>Chi Square

<sup>‡‡</sup>Independently reviewed cohort - Gemcitabine/Carboplatin N=121, Carboplatin N=101

##### Breast Cancer:

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

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

Table 4: Gemcitabine plus Paclitaxel and Paclitaxel in Breast Cancer

	Gemcitabine/ Paclitaxel	Paclitaxel
Number of patients	267	262
Median age, years	53	52
Range	26 to 83	26 to 75
Metastatic disease	97.0%	96.9%
Baseline KPS <sup>‡</sup> ≥90	70.4%	74.4%
Number of tumor sites 1-2 ≥3	56.6% 43.4%	58.8% 41.2%
Visceral disease	73.4%	72.9%
Prior anthracycline	96.6%	95.8%
<b>Overall Survival<sup>¶</sup></b>		
Median (95%, CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)

Hazard Ratio (95%, CI)	0.86 (0.71, 1.04)		
Time to Documented Disease			
Progression Median (95%, C.I.), months	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)	p<0.0001
Hazard Ratio (95%, C.I.)	0.650 (0.524, 0.805)		p<0.0001
Overall Response Rate <sup>‡</sup> (95%, C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)	p<0.0001

\*Karnofsky Performance Status.

<sup>‡</sup>Based on the ITT population

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

##### Non-Small Cell Lung Cancer (NSCLC):

Data from 2 randomized clinical studies (657 patients) support the use of Gemcitabine in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC.

*Gemcitabine plus cisplatin versus cisplatin:* This study was conducted in Europe, the US, and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemcitabine 1000 mg/m<sup>2</sup> was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m<sup>2</sup> administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m<sup>2</sup> was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 13. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the Gemcitabine plus cisplatin arm having adenocarcinoma.

Median survival time on the Gemcitabine plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Log rank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Gemcitabine plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank p=0.009, two-sided). The objective response rate on the Gemcitabine plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed.

*Gemcitabine plus cisplatin versus etoposide plus cisplatin:*

A second, multicenter, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8, and cisplatin 100 mg/m<sup>2</sup> on Day 1 of a 21-day cycle or to etoposide 100 mg/m<sup>2</sup> IV on Days 1, 2, and 3 and cisplatin 100 mg/m<sup>2</sup> on Day 1 of a 21-day cycle (Table 13).

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

*Quality of Life (QOL):*

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

Table 5: Randomized trial of combination therapy with Gemcitabine and Cisplatin in NSCLC

Trial	28-day Schedule*		21-day Schedule*			
	Gemcitabine/ Cisplatin	Cisplatin	Gemcitabine/ Cisplatin	Cisplatin/ Etoposide		
Number of patients	260	262	69	66		
Male	182	186	64	61		
Female	78	76	5	5		
Median age, years	62	63	58	60		
Range	36 to 88	35 to 79	33 to 76	35 to 75		
Stage IIIA	7%	7%	N/A <sup>‡</sup>	N/A <sup>‡</sup>		
Stage IIIB	26%	23%	48%	52%		
Stage IV	67%	70%	52%	49%		
Baseline KPSd	41%	44%	45%	52%		
70 to 80						
Baseline KPSd	57%	55%	55%	49%		
90 to 100						
Survival		p=0.008		p=0.18		
Median, months	9.0	7.6	8.7	7.0		
(95%, C.I.)	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.)	4.2, 5.7	3.0, 4.3	4.2, 6.4	2.4, 4.5		
Tumor Response	26%	10%	p<0.0001*	33%	14%	p=0.01*

\*28-day schedule — Gemcitabine plus cisplatin: Gemcitabine 1000 mg/m<sup>2</sup> on Days 1, 8, and 15 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 every 28 days. 628

<sup>‡</sup>21-day schedule — Gemcitabine plus cisplatin: Gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 and cisplatin 100 mg/m<sup>2</sup> on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m<sup>2</sup> on Day 1 and IV etoposide 100 mg/m<sup>2</sup> on Days 1, 2, and 3 every 21 days.

<sup>‡‡</sup>N/A Not applicable.

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

<sup>‡‡‡‡</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.

**Pancreatic Cancer:** Data from 2 clinical trials evaluated the use of Gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Gemcitabine to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of Gemcitabine in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemcitabine 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 Gemcitabine. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response," which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables

were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:

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

OR:

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

The first study was a multicenter (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemcitabine and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/ m<sup>2</sup> for 30 minutes. Patients treated with Gemcitabine had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU.

Table 6: Gemcitabine Verses 5-FU in Pancreatic Cancer

	Gemcitabine	5-FU	
Number of patients	63	63	
Male	34	34	
Female	29	29	
Median age	62 years	61 years	
Range	37 to 79	36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS <sup>‡</sup> ≤70	69.8%	68.3%	
Clinical benefit response	22.2% (N=14)	4.8% (N=3)	p=0.004*
Survival			p=0.0009
Median	5.7 months	4.2 months	
6-month probability <sup>‡</sup>	(N=30) 46%	(N=19) 29%	
9-month probability <sup>‡</sup>	(N=14) 24%	(N=4) 5%	
1-year probability <sup>‡</sup>	(N=9) 18%	(N=2) 2%	
Range	0.2 to 18.6 months	0.4 to 15.1+d 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+d months	
95% C.I. of the median	1.9 to 3.4 months	0.9 to 1.1 months	

\*Karnofsky Performance Status.

<sup>‡</sup>Kaplan-Meier estimates.

<sup>‡‡</sup>N=number of patients. 665 <sup>‡‡‡</sup>No progression at last visit; remains alive.

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

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

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

##### Bladder Cancer:

A randomized phase III study of 405 patients with advanced or metastatic urothelial transitional cell carcinoma showed no difference between the two treatment arms, gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin (MVAC), in term of median survival (12.8 and 14.8 months respectively, p=0.547), time to disease progression (7.4 and 7.6 months respectively, p=0.842) and response rate (49.4% and 45.7% respectively, p=0.512). However, the combination of gemcitabine and cisplatin had a better toxicity profile than MVAC.

##### Biliary Tract Cancer:

Valle Juan et al., randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter on days 1 and 8, every 3 weeks for eight cycles) or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.

After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin-gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001). The median progression-free survival was 8.0 months in the cisplatin-gemcitabine group and 5.0 months in the gemcitabine-only group (P<0.001). In addition, the rate of tumor control among patients in the cisplatin-gemcitabine group was significantly increased (81.4% vs. 71.8%, P = 0.049). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin-gemcitabine group; the number of neutropenia-associated infections was similar in the two groups.

As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer.

##### Other Clinical Studies:

When Gemcitabine was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of Gemcitabine to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above



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with Gemcitabine plus cisplatin compared to one (<1%) Grade 3 dysrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the Gemcitabine plus cisplatin combination arm.

Table 9 presents data from the randomized study of Gemcitabine plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC for the same WHO-graded adverse events as those in Table 9. One death (1.5%) was reported on the Gemcitabine plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the Gemcitabine plus cisplatin arm was less than on the etoposide plus cisplatin arm (28% versus 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the Gemcitabine plus cisplatin arm. RBC transfusions were given to 29% of the patients who received Gemcitabine plus cisplatin versus 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received Gemcitabine plus cisplatin versus 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the Gemcitabine plus cisplatin arm. On the Gemcitabine plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of Gemcitabine as compared to etoposide, which may explain the differences in the incidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the Gemcitabine plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemcitabine plus cisplatin arm reported edema compared to one patient (2%) on the etoposide plus cisplatin arm.

**Table 8: Selected WHO-Graded Adverse Events From Comparative Trial of Gemcitabine Plus Cisplatin Versus Single-Agent Cisplatin in NSCLC CTC Grades (% incidence)\***

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

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

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

<sup>a</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 28 days.

<sup>a</sup>Regardless of causality

**Table 9: Selected WHO-Graded Adverse Reactions From Comparative Trial of Gemcitabine Plus Cisplatin Versus Etoposide Plus Cisplatin in NSCLC WHO Grades (% incidence)<sup>a</sup>**

	Gemcitabine plus Cisplatin <sup>a</sup>			Etoposide plus Cisplatin <sup>a</sup>		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Laboratory<sup>a</sup></b>						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions <sup>a</sup>	29	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>a</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
Non-laboratory <sup>a</sup>						
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
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Allopecia	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

<sup>a</sup>Grade based on criteria from the World Health Organization (WHO).

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

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

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

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

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

<sup>a</sup>Pain data were not collected.

**Combination Use in Breast Cancer:**

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

Table 10 presents the safety data occurrences of ≥10% (all grades) from the Gemcitabine plus paclitaxel versus paclitaxel study in breast cancer.

**Table 10: Adverse Events from Comparative Trial of Gemcitabine Plus Paclitaxel Versus Single-Agent Paclitaxel in Breast Cancer<sup>a</sup> CTC Grades (% incidence)**

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

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

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

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

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

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

**Combination Use in Ovarian Cancer:**

In the Gemcitabine plus carboplatin versus carboplatin study, dose reductions occurred with 10.4% of Gemcitabine injections and 1.8% of carboplatin injections on the combination arm, versus 3.8% on the carboplatin alone arm. On the combination arm, 13.7% of Gemcitabine doses were omitted and 0.2% of carboplatin doses were omitted, compared to 0% of carboplatin doses on the carboplatin alone arm. There were no differences in discontinuations due to adverse events between arms (10.9% versus 9.8%, respectively).

Table 11 presents the adverse events (all grades) occurring in ≥10% of patients in the ovarian cancer study.

**Table 11: Adverse Events from Comparative Trial of Gemcitabine Plus Carboplatin Versus Single-Agent Carboplatin in Ovarian Cancer<sup>a</sup> CTC Grades (% incidence)**

	Gemcitabine plus Carboplatin			Carboplatin		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
	(N=175)			(N=174)		
<b>Laboratory<sup>a</sup></b>						
Hematologic						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Leukopenia	86	48	5	70	6	<1
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusions <sup>a</sup>	38			15		
Platelet Transfusions <sup>a</sup>	9			3		
<b>Non-laboratory<sup>a</sup></b>						
Nausea	69	6	0	61	3	0
Allopecia	49	0	0	17	0	0

Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Neuropathy–sensory	29	1	0	27	2	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0
Anorexia	16	1	0	13	0	0

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

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

<sup>a</sup>Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red blood cells and whole blood.

In addition to blood product transfusions as listed in Table 12, myelosuppression was also managed with hematopoietic agents. These agents were administered more frequently with combination therapy than with monotherapy (granulocyte growth factors: 23.6% and 10.1%, respectively; erythropoietic agents: 7.3% and 3.9%, respectively).

The following are the clinically relevant adverse events, regardless of causality, that occurred in >1% and <10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse events (Gemcitabine plus carboplatin versus carboplatin): AST or ALT elevation (0 versus 1.2%), dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1%), hypersensitivity reaction (2.3% versus 2.9%), motor neuropathy (1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

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

**DRUG INTERACTIONS:**

No specific drug interaction studies have been conducted. Information is available on the pharmacodynamics and pharmacokinetics of Gemcitabine in combination with cisplatin, paclitaxel, or carboplatin

**Post-Marketing Experience:**

The following adverse reactions have been identified during post-approval use of Gemcitabine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions have occurred after Gemcitabine single-agent use and Gemcitabine in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemcitabine.

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

*Vascular Disorders* — Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.

*Skin* — Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported. Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

*Hepatic* — Increased liver function tests including elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemcitabine alone or in combination 392 with other potentially hepatotoxic drugs.

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

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

*Injury, Poisoning, and Procedural Complications* — Radiation recall reactions have been reported.

**WARNINGS:**

**Infusion Time:**

**Caution:** Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing has been shown to increase toxicity.

**Hematology:** Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia, and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy.

**Pulmonary:** Pulmonary toxicity has been reported with the use of Gemcitabine. In cases of severe lung toxicity, Gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

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

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

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

**Laboratory Tests:**

Patients receiving Gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected. Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter

**Radiation Therapy:**

A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and 166 non-concurrent use of Gemcitabine.

*Non-concurrent (given >7 days apart)* — Analysis of the data does not indicate enhanced toxicity when Gemcitabine is administered more than 7