HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Gemcitabine for Injection, USP safely and effectively. See full prescribing information for Gemcitabine for Injection, USP.

Gemcitabine for Injection, USP, Powder, Lyophilized, For Solution For Intravenous Use

Initial U.S. Approval: 1996

--------INDICATIONS AND USAGE---------
Gemcitabine for Injection, USP is a nucleoside metabolic inhibitor indicated for:
- Ovarian cancer in combination with carboplatin (1.1)
- Breast cancer in combination with paclitaxel (1.2)
- Non-small cell lung cancer in combination with cisplatin (1.3)
- Pancreatic cancer as a single-agent (1.4)

-----DOSAGE AND ADMINISTRATION-----
Gemcitabine for Injection, USP is for intravenous use only.
- Ovarian cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.1)
- Breast cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.2)
- Non-small cell lung cancer: 4-week schedule, 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle: 3-week schedule; 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle (2.3)
- Pancreatic cancer: 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks (2.4)
- Dose Reductions or discontinuation may be needed based on toxicities (2.1 to 2.4)

---DOSAGE FORMS AND STRENGTHS---
- 200 mg vial for injection (3)
- 1 g vial for injection (3)

---------CONTRAINDICATIONS----------
Patients with a known hypersensitivity to gemcitabine (4)

-----WARNINGS AND PRECAUTIONS-----
- Infusion time and dose frequency: Increased toxicity with infusion time >60 minutes or dosing more frequently than once weekly. (5.1)
- Hematology: Monitor for myelosuppression, which can be dose-limiting. (5.2, 5.7)
- Pulmonary toxicity: Discontinue Gemcitabine for Injection, USP immediately for severe pulmonary toxicity. (5.3)
- Renal: Monitor renal function prior to initiation of therapy and periodically thereafter. Use with caution in patients with renal impairment. Cases of hemolytic uremic syndrome (HUS) and/or renal failure, some fatal, have occurred. Discontinue Gemcitabine for Injection, USP for HUS or severe renal toxicity. (5.4)
- Hepatic: Monitor hepatic function prior to initiation of therapy and periodically thereafter. Use with caution in patients with hepatic impairment. Serious hepatotoxicity, including liver failure and death, have occurred. Discontinue Gemcitabine for Injection, USP for severe hepatic toxicity. (5.5)
- Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus. (5.6, 8.1)
- Radiation toxicity. May cause severe and life-threatening toxicity. (5.8)

----------ADVERSE REACTIONS----------
The most common adverse reactions for the single-agent (≥20%) are nausea and vomiting, anemia, ALT, AST, neutropenia, leukopenia, alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
1.1 Ovarian Cancer
Gemcitabine for Injection, USP in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.

1.2 Breast Cancer
Gemcitabine for Injection, USP in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

1.3 Non-Small Cell Lung Cancer
Gemcitabine for Injection, USP is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

1.4 Pancreatic Cancer
Gemcitabine for Injection, USP is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine for Injection, USP is indicated for patients previously treated with 5-FU.

2 DOSAGE AND ADMINISTRATION
Gemcitabine for Injection, USP is for intravenous use only. Gemcitabine for Injection, USP may be administered on an outpatient basis.

2.1 Ovarian Cancer
Gemcitabine for Injection, USP should be administered intravenously at a dose of 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after Gemcitabine for Injection, USP administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.

Dose Modifications
Gemcitabine for Injection, USP dosage adjustment for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemcitabine for Injection, USP dosage should be modified according to guidelines in Table 1.

Table 1: Day 8 Dosage Reduction Guidelines for Gemcitabine for Injection, USP in Combination with Carboplatin

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1500	And	≥100,000	100
1000 to 1499	and/or	75,000 to 99,999	50
<1000	and/or	<75,000	Hold

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

Dose adjustment for Gemcitabine for Injection, USP in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of Gemcitabine for Injection, USP in subsequent cycles should be reduced to 800 mg/m^2 on Days 1 and 8 in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10^6/L for more than 5 days
- Absolute granulocyte count <100 x 10^6/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10^6/L
- Cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction, for the subsequent cycle, Gemcitabine for Injection, USP should be given on Day 1 only at 800 mg/m^2.

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

Dose Modifications
Gemcitabine for Injection, USP dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemcitabine for Injection, USP dosage should be modified according to the guidelines in Table 2.

Table 2: Day 8 Dosage Reduction Guidelines for Gemcitabine for Injection, USP 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 to 1199	Or	50,000 to 75,000	75
700 to 999	And	≥50,000	50
<700	Or	<50,000	Hold

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

2.3 Non-Small Cell Lung Cancer
Two schedules have been investigated and the optimum schedule has not been determined *[see Clinical Studies (14.3)]*. With the 4-week schedule, Gemcitabine for Injection, USP should be administered intravenously at 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m^2 on Day 1 after the infusion of Gemcitabine for Injection, USP. With the 3-week schedule, Gemcitabine for Injection, USP should be administered intravenously at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m^2 should be administered intravenously after the infusion of Gemcitabine for Injection, USP on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications
Dosage adjustments for hematologic toxicity may be required for Gemcitabine for Injection, USP and for cisplatin. Gemcitabine for Injection, USP dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemcitabine for Injection, USP should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3. For cisplatin dosage adjustment, see manufacturer's prescribing information.

In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine for Injection, USP plus cisplatin should be held or decreased by 50% depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grade 3/4 serum creatinine toxicity for Gemcitabine for Injection, USP plus cisplatin was 5% versus 2% for cisplatin alone).

2.4 Pancreatic Cancer
Gemcitabine for Injection, USP should be administered by intravenous infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications
Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient *[see Warnings and Precautions (5.2)]*. Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

Patients receiving Gemcitabine for Injection, USP should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3.

Table 3: 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 to 999	Or	50,000 to 99,999	75
<500	Or	<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine for Injection, USP should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

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

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

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published *[see References (15)]*.

2.6 Preparation for Intravenous Infusion Administration
The recommended diluent for reconstitution of Gemcitabine for Injection, USP is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemcitabine for Injection, USP upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

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

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

When prepared as directed, Gemcitabine for Injection, USP solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Discard unused portion. Solutions of reconstituted Gemcitabine for Injection, USP should not be refrigerated, as crystallization may occur.

The compatibility of Gemcitabine for Injection, USP with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS
Gemcitabine for Injection, USP is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

4 CONTRAINDICATIONS
Gemcitabine for Injection, USP is contraindicated in those patients with a known hypersensitivity to the drug.

5 WARNINGS AND PRECAUTIONS
Patients receiving therapy with Gemcitabine for Injection, USP should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.

5.1 Infusion Time
Caution - Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity *[see Clinical Studies (14.5)]*.

5.2 Hematology
Gemcitabine for Injection, USP can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia *[see Adverse Reactions (6.1)]*, and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.

5.3 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 *[see Adverse Reactions (6.1 and 6.2)]*.

5.4 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 reported. The majority of the cases of renal failure leading to death were due to HUS *[see Adverse Reactions (6.1 and 6.2)]*.

Gemcitabine should be used with caution in patients with preexisting renal impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations *[see Use in Specific Populations (8.6)]*.

5.5 Hepatic
Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs *[see Adverse Reactions (6.1 and 6.2)]*.

Gemcitabine should be used with caution in patients with preexisting hepatic insufficiency as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. Administration of gemcitabine in patients with concurrent liver metastases or a preexisting medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency *[see Use in Specific Populations (8.7)]*.

5.6 Pregnancy
Gemcitabine for Injection, USP can cause fetal harm when administered to a pregnant woman. In pre-clinical studies in mice and rabbits, gemcitabine was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of Gemcitabine for Injection, USP in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.7 Laboratory Tests
Patients receiving Gemcitabine for Injection, USP should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.

Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter *[see Dosage and Administration (2.4)]*.

5.8 Radiation Therapy
A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and 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 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

Concurrent (given together or ≤7 days apart) - Preclinical and clinical studies have shown that gemcitabine has radiosensitizing activity. Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. In a single trial, where gemcitabine at a dose of 1000 mg/m^2 was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life-threatening mucositis, especially esophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4795 cm^3]. Subsequent studies have been reported and suggest that gemcitabine administered at lower doses with concurrent radiotherapy has predictable and less severe toxicity. However, the optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumor types.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Most adverse reactions are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

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

Single-Agent Use:
Myelosuppression is the principal dose-limiting toxicity with gemcitabine therapy. Dosage adjustments for hematologic toxicity are frequently needed *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.

The data in Table 4 are based on 979 patients receiving gemcitabine as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The gemcitabine starting doses ranged from 800 to 1250 mg/m^2. Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO Grade 3 or 4) adverse reactions were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of gemcitabine therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the gemcitabine arm and 4.8% for the 5-FU arm. All WHO-graded laboratory adverse reactions are listed in Table 4, regardless of causality. Non-laboratory adverse reactions listed in Table 4 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific adverse reactions under the Renal, Pulmonary, and Infection categories.

Table 4: Selected WHO-Graded Adverse Reactions in Patients Receiving Single-Agent Gemcitabine WHO Grades (% incidence)[a]

	All Patients[b]			Pancreatic Cancer Patients[c]			Discontinuations (%)[d]
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory[e]							
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[f]							
Nausea and Vomiting	69	13	1	71	10	2	<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
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

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=699 to 974; all patients with laboratory or non-laboratory data.
[c] N=161 to 241; all pancreatic cancer patients with laboratory or non-laboratory data.
[d] N=979.
[e] Regardless of causality.
[f] Table includes non-laboratory data with incidence for all patients ≥10%. For approximately 60% of the patients, non-laboratory adverse reactions were graded only if assessed to be possibly drug-related.

Hematologic - In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with gemcitabine, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.

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

Hepatic - In clinical trials, gemcitabine was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to gemcitabine or with greater total cumulative dose. 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 *[see Adverse Reactions (6.2)]*.

Renal - In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving gemcitabine in clinical trials. Four patients developed HUS on gemcitabine therapy, 2 immediately posttherapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required *[see Adverse Reactions (6.2)]*.

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

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

Pulmonary - In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of gemcitabine *[see Adverse Reactions (6.2)]*. The etiology of these effects is unknown. If such effects develop, gemcitabine should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

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

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

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

Alopecia - Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity - There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation - Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemcitabine is not a vesicant.

Allergic - Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemcitabine should not be administered to patients with a known hypersensitivity to this drug *[see Contraindications (4)]*.

Cardiovascular - During clinical trials, 2% of patients discontinued therapy with gemcitabine due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease *[see Adverse Reactions (6.2)]*.

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

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

Table 5 presents the safety data from the gemcitabine plus cisplatin versus cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. The two-drug combination was more myelosuppressive with 4 (1.5%) possibly treatment-related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the gemcitabine plus cisplatin arm.

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

Nausea and vomiting despite the use of antiemetics occurred more often with gemcitabine plus cisplatin therapy (78%) than with cisplatin alone (71%). In studies with single-agent gemcitabine, a lower incidence of nausea and vomiting (58% to 69%) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with gemcitabine plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

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

Table 6 presents data from the randomized study of gemcitabine plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC. 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 5: Selected CTC-Graded Adverse Reactions From Comparative Trial of Gemcitabine Plus Cisplatin Versus Single-Agent Cisplatin in NSCLC

CTC Grades (% incidence)[a]

	Gemcitabine plus Cisplatin[b]			Cisplatin[c]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						
Hematologic						
Anemia	89	22	3	67	6	1
RBC Transfusion[e]	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[e]	21			<1		
Lymphocytes	75	25	18	51	12	5
Hepatic						
Transaminase	22

Table 8 presents the adverse reactions (all grades) occurring in ≥10% of patients in the ovarian cancer study.

Table 8: Adverse Reactions From Comparative Trial of Gemcitabine Plus Carboplatin Versus Single-Agent Carboplatin in Ovarian Cancer[a]

CTC Grades (% incidence)

	Gemcitabine plus Carboplatin (N=175)			Carboplatin (N=174)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[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[c]	38			15		
Platelet Transfusions[c]	9			3		
Non-laboratory[b]						
Nausea	69	6	0	61	3	0
Alopecia	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

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%).
[b] Regardless of causality.
[c] 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 8, 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 reactions, 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 reactions (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.

6.2 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 with other potentially hepatotoxic drugs. Hepatic veno-occlusive disease has been reported.

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 *[see Warnings and Precautions (5.8)]*.

7 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 *[see Clinical Pharmacology (12.2 and 12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category D. See 'Warnings and Precautions' section.

Gemcitabine for Injection, USP can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, gemcitabine is expected to result in adverse reproductive effects. There are no adequate and well-controlled studies of gemcitabine in pregnant women. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.6)]*.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Gemcitabine for Injection, USP, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of gemcitabine in pediatric patients has not been established. Gemcitabine was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one-week rest period. Gemcitabine was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m^2/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

8.5 Geriatric Use
Gemcitabine clearance is affected by age *[see Clinical Pharmacology (12.3)]*. There is no evidence, however, that unusual dose adjustments *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]* are necessary in patients over 65, and in general, adverse reaction rates in the single-agent safety database of 979 patients were similar in patients above and below 65. Grade 3/4 thrombocytopenia was more common in the elderly. In the randomized clinical trial of gemcitabine in combination with carboplatin for recurrent ovarian cancer *[see Clinical Studies (14.1)]*, 125 women treated with gemcitabine plus carboplatin were <65 years and 50 were ≥65 years. Similar effectiveness was observed between older and younger women. There was significantly higher Grade 3/4 neutropenia in women 65 years of age or older. Overall, there were no other substantial differences in toxicity profile of gemcitabine plus carboplatin based on age.

8.6 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 reported. The majority of the cases of renal failure leading to death were due to HUS *[see Adverse Reactions (6.1 and 6.2)]*.

Gemcitabine for Injection, USP should be used with caution in patients with preexisting renal impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations *[see Warnings and Precautions (5.4)]*.

8.7 Hepatic
Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs *[see Adverse Reactions (6.1 and 6.2)]*.

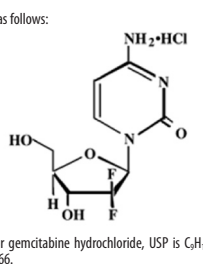
Gemcitabine should be used with caution in patients with preexisting hepatic insufficiency as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. Administration of gemcitabine in patients with concurrent liver metastases or a preexisting medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency *[see Warnings and Precautions (5.5)]*.

8.8 Gender
Gemcitabine clearance is affected by gender *[see Clinical Pharmacology (12.3)]*. In the single-agent safety database (N=979 patients), however, there is no evidence that unusual dose adjustments *[see Dosage and Administration (2)]* are necessary in women. In general, in single-agent studies of gemcitabine, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia. There was a greater tendency in women, especially older women, not to proceed to the next cycle.

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

11 DESCRIPTION
Gemcitabine for Injection, USP is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine Hydrochloride, USP is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine hydrochloride, USP is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66.

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

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemcitabine for Injection, USP contain either 200 mg or 1 g of gemcitabine hydrochloride, USP (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Sodium hydroxide may have been added for pH adjustment.

12 CLINICAL PHARMACOLOGY
12.1 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-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

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

12.3 Pharmacokinetics
Absorption and Distribution
The pharmacokinetics of gemcitabine were examined in 353 patients, 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^2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m^2.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

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

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.

Excretion
Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. 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 9 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 9: Gemcitabine Clearance and Half-Life for the "Typical" Patient

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

[a] Half-life for patients receiving a short infusion (<70 min).

Gemcitabine half-life for short infusions ranged from 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.

Drug Interactions
When gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours *[see Drug Interactions (7)]*. Analysis of data from metastatic breast cancer patients shows that, on average, gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine. Data from NSCLC patients demonstrate that gemcitabine and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies to evaluate the carcinogenic potential of gemcitabine have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vivo* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day administered intravenously (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the human dose on a mg/m^2 basis).

14 CLINICAL STUDIES
14.1 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^2 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 10. The addition of gemcitabine to carboplatin resulted in statistically significant improvement in PFS and overall response rate as shown in Table 11 and Figure 1. 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 10: 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 to 81
Baseline ECOG performance status 0 to 1[a]	94%	95%
Disease Status Evaluable Bidimensionally measurable	 7.9% 91.6%	 2.8% 95.5%
Platinum-free interval[b] 6 to 12 months >12 months	 39.9% 59.0%	 39.9% 59.6%
First-line therapy Platinum-taxane combination Platinum-non-taxane combination Platinum monotherapy	 70.2% 28.7% 1.1%	 71.3% 27.5% 1.1%

[a] 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.
[b] 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 11: Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Results of Efficacy Analysis

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

[a] Treatment adjusted for performance status, tumor area, and platinum-free interval.
[b] Partial response non-measurable disease
[c] Independent reviewers could not evaluate disease demonstrated by sonography or physical exam.
[d] Log Rank, unadjusted
[e] Chi Square
[f] Independently reviewed cohort - Gemcitabine/Carboplatin N=121, Carboplatin N=101

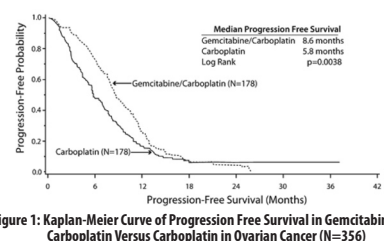


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemcitabine Plus Carboplatin Versus Carboplatin in Ovarian Cancer (N=356)

14.2 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^2 was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m^2 administered prior to gemcitabine on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle as the control arm.

The addition of gemcitabine to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to monotherapy with paclitaxel as shown in Table 12 and Figure 2. Final survival analysis results at 440 events were Hazard Ratio of 0.86 (95%, CI: 0.71 to 1.04) for the ITT population, as shown in Table 12.

Table 12: Gemcitabine Plus Paclitaxel Versus 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[a] ≥90	70.4%	74.4%	
Number of tumor sites 1 to 2 ≥3	 56.6% 43.4%	 58.8% 41.2%	
Visceral disease	73.4%	72.9%	
Prior anthracycline	96.6%	95.8%	
Overall Survival[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[c] 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[c] (95%, C.I.)	 40.8% (34.9, 46.7)	 22.1% (17.1, 27.2)	p<0.0001

[a] Karnofsky Performance Status.
[b] Based on the ITT population
[c] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

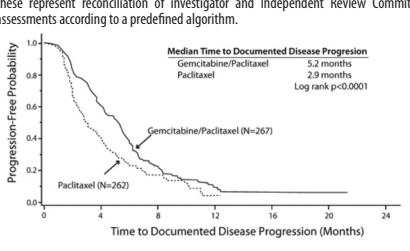


Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemcitabine Plus Paclitaxel Versus Paclitaxel Breast Cancer Study (N=529)

14.3 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^2 was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m^2 was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 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.

The Kaplan-Meier survival curve is shown in Figure 3. 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^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to intravenous etoposide 100 mg/m^2 on Days 1, 2, and 3 and cisplatin 100 mg/m^2 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).

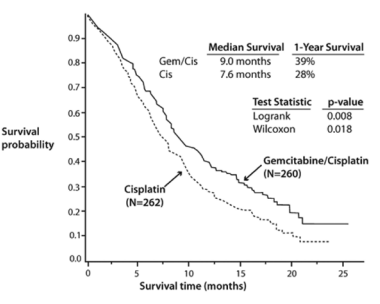


Figure 3: Kaplan-Meier Survival Curve in Gemcitabine Plus Cisplatin Versus Cisplatin NSCLC Study (N=522)

Table 13: Randomized Trials of Combination Therapy With Gemcitabine Plus Cisplatin in NSCLC

Trial	28-day Schedule[a]			21-day Schedule[b]		
Treatment Arm	Gemcitabine/ Cisplatin	Cisplatin		Gemcitabine/ Cisplatin	Cisplatin/ Etoposide	
Number of patients Male Female	260 182 78	262 186 76		69 64 5	66 61 5	
Median age, years Range	62 36 to 88	63 35 to 79		58 33 to 76	60 35 to 75	
Stage IIIA Stage IIIB Stage IV	7% 26% 67%	7% 23% 70%		N/A[c] 48% 52%	N/A[c] 52% 49%	
Baseline KPS[d] 70 to 80 Baseline KPS[d] 90 to 100	41% 57%	44% 55%		45% 55%	52% 49%	
Survival Median, months (95%, C.I.) months	 9.0 8.2, 11.0	 7.6 6.6, 8.8	p=0.008	 8.7 7.8, 10.1	 7.0 6.0, 9.7	p=0.18
Time to Disease Progression Median, months (95%, C.I.) months	 5.2 4.2, 5.7	 3.7 3.0, 4.3	p=0.009	 5.0 4.2, 6.4	 4.1 2.4, 4.5	p=0.015
Tumor Response	26%	10%	p<0.0001[e]	33%	14%	p=0.01[e]

[a] 28-day schedule - Gemcitabine plus cisplatin: Gemcitabine 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 100 mg/m^2 on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m^2 on Day 1 every 28 days.
[b] 21-day schedule - Gemcitabine plus cisplatin: Gemcitabine 1250 mg/m^2 on Days 1 and 8 and cisplatin 100 mg/m^2 on Day 1 every 21 days; Etoposide plus Cisplatin: cisplatin 100 mg/m^2 on Day 1 and intravenous etoposide 100 mg/m^2 on Days 1, 2, and 3 every 21 days.
[c] N/A Not applicable.
[d] Karnofsky Performance Status.
[e] 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.

14.4 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^2 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^2 for 30 minutes. The results from this randomized trial are shown in Table 14. Patients treated with gemcitabine had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 4. No confirmed objective tumor responses were observed with either treatment.

Table 14: Gemcitabine Versus 5-FU in Pancreatic Cancer

	Gemcitabine	5-FU	
Number of patients Male Female	63 34 29	63 34 29	
Median age Range	62 years 37 to 79	61 years 36 to 77	
Stage IV disease	71.4%	76.2%	
Baseline KPS[a] ≤70	69.8%	68.3%	
Clinical benefit response	22.2% (N[c]=14)	4.8% (N[c]=3)	p=0.004[e]
Survival Median 6-month probability[b] 9-month probability[b] 1-year probability[b] Range 95% C.I. of the median	 5.7 months (N=30) 46% (N=14) 24% (N=9) 18% 0.2 to 18.6 months 4.7 to 6.9 months	 4.2 months (N=19) 29% (N=4) 5% (N=2) 2% 0.4 to 15.1+[d] months 3.1 to 5.1 months	p=0.0009
Time to Disease Progression Median Range 95% C.I. of the median	 2.1 months 0.1+[d] to 9.4 months 1.9 to 3.4 months	 0.9 months 0.1 to 12.0+[d] months 0.9 to 1.1 months	p=0.0013

[a] Karnofsky Performance Status.
[b] Kaplan-Meier estimates.
[c] N=number of patients.
[d] No progression at last visit; remains alive.
[e] The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the 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.

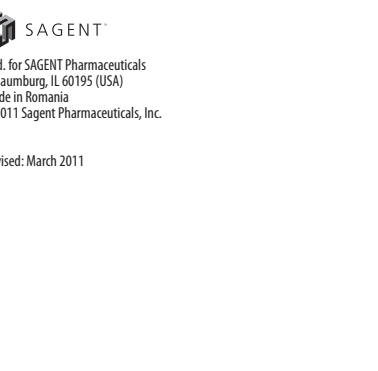


Figure 4: Kaplan-Meier Survival Curve

The second trial was a multi-center (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.

14.5 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 10 mg/m^2. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m^2 (30-minute infusion) and 150 mg/m^2 (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m^2 at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion *[see Clinical Pharmacology (12.3)]* and the toxicity appears to be increased if gemcitabine is administered more frequently than once weekly or with infusions longer than 60 minutes *[see Warnings and Precautions (5.1)]*.

15 REFERENCES

1. NIOSH Alert: Preventing occup