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

----------------------RECENT MAJOR CHANGES ------------------------

Dosage and Administration:
Dose Modifications for Non-Hematologic Adverse Reactions (2.5) 06/2014
Warnings and Precautions:
Posterior Reversible Encephalopathy Syndrome (5.9) 06/2014

-------------------------INDICATIONS AND USAGE ----------------------

Gemcitabine for Injection, USP is a nucleoside metabolic inhibitor indicated:

- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. (1.1)
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. (1.2)
- in combination with cisplatin for the treatment of non-small cell lung cancer. (1.3)
- as a single agent for the treatment of pancreatic cancer. (1.4)

------------------DOSAGE AND ADMINISTRATION-------------------

Gemcitabine is for intravenous use only.

- Ovarian Cancer: 1,000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.1)
- Breast Cancer: 1,250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.2)
- Non-Small Cell Lung Cancer: 1,000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.3)
- Pancreatic Cancer: 1,000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle. (2.4)

---------------------DOSAGE FORMS AND STRENGTHS -------------

- 200 mg/single-use vial (3)
- 1 g/single-use vial (3)
- 2 g/single-use vial (3)

---------------------------CONTRAINDICATIONS------------------------

Patients with a known hypersensitivity to gemcitabine. (4)

-------------------WARNINGS AND PRECAUTIONS -------------------

- Schedule-dependent toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly. (5.1)
- Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression. (5.2, 5.7)
- Pulmonary Toxicity and Respiratory Failure: Discontinue gemcitabine immediately for unexplained new or worsening dyspnea or evidence of severe pulmonary toxicity. (5.3)
- Hemolytic-Uremic Syndrome (HUS): Monitor renal function prior to initiation and during therapy. Discontinue gemcitabine for HUS or severe renal impairment. (5.4)
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during therapy. Discontinue gemcitabine for severe hepatic toxicity. (5.5)
- Embryofetal Toxicity: Can cause fetal harm. Advise women of potential risk to the fetus. (5.6, 8.1)
- Exacerbation of Radiation Therapy Toxicity: May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy. (5.7)
- Capillary Leak Syndrome: Discontinue gemcitabine. (5.8)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue gemcitabine. (5.9)

-----------------------ADVERSE REACTIONS ------------------------

The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance & Medical Affairs at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/ medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 01/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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 is indicated for patients previously treated with 5-FU.

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of gemcitabine for injection is 1, 000 mg/m^2 as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after gemcitabine for injection, USP administration on Day 1 of each 21-day cycle. Refer to carboplatin prescribing information for additional information.

Dose Modifications

Recommended gemcitabine for injection dose modifications for myelosuppression are described in Table 1 and Table 2 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 1: Dosage Reduction Guidelines for Gemcitabine for Injection for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
Day 1	≥1,500	and	≥100,000	100%
	<1,500	or	<100,000	Delay Treatment Cycle
Day 8	≥1,500	and	≥100,000	100%
	1,000 to1,499	or	75,000 to 99,999	50%
	<1,000	or	<75,000	Hold

Table 2: Gemcitabine for Injection Dose Modification for Myelosuppression in Previous Cycle In Ovarian Cancer

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial Occurrence	Absolute granulocyte count less than 500 x 10^6/L for more than 5 days Absolute granulocyte count less than 100 x 10^6/L for more than 3 days Febrile neutropenia Platelets less than 25,000x10^6/L Cycle delay of more than one week due to toxicity	Permanently reduce gemcitabine to 800 mg/m^2 on Days 1 and 8
Subsequent Occurrence	If any of the above toxicities occur after the initial dose reduction	Permanently reduce gemcitabine for injection dose to 800 mg/m^2 on Day 1 only

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of gemcitabine for injection is 1,250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3 hour intravenous infusion before gemcitabine for injection, USP administration.

Dose Modifications

Recommended dose modifications for gemcitabine for injection for myelosuppression are described in Table 3 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Table 3: Recommended Dose Reductions for Gemcitabine for Injection for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
Day 1	≥1,500	and	≥100,000	100%
	less than 1,500	or	less than 100,000	Hold
Day 8	≥1,200	and	>75,000	100%
	1,000 to1,199	or	50,000 to 75,000	75%
	700 to 999	and	≥50,000	50%
	<700	or	<50,000	Hold

2.3 Non-Small Cell Lung Cancer

Recommended Dose and Schedule

Every 4-week schedule

The recommended dose of gemcitabine for injection is 1,000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of gemcitabine for injection.

Every 3-week schedule

The recommended dose of gemcitabine for injection is 1,250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m^2 on Day 1 after the infusion of gemcitabine for injection.

Dose Modifications

Recommended dose modifications for gemcitabine for injection myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for gemcitabine for injection recommendations for non-hematologic adverse reactions.

2.4 Pancreatic Cancer

Recommended Dose and Schedule

The recommended dose of gemcitabine for injection is 1,000 mg/m^2 over 30 minutes intravenously. The recommended treatment schedule is as follows:

- Weeks 1 to 8: weekly dosing for the first 7 weeks followed by one week rest.
- After week 8: weekly dosing on Days 1, 8, and 15 of 28-day cycles.

Dose Modifications

Recommended dose modifications for gemcitabine for injection for myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to Dosage and Administration (2.5) for recommendations for non-hematologic adverse reactions.

Patients receiving gemcitabine for injection 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 4.

Table 4: Recommended Dose Reductions for Gemcitabine for Injection for Myelosuppression in Pancreatic Cancer and Non-Small Cell Lung Cancer

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥1,000	And	≥100,000	100 %
500 to 999	Or	50,000 to 99,999	75 %
<500	Or	<50,000	Hold

2.5 Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue gemcitabine for injection for any of the following

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Withhold gemcitabine for injection or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

2.6 Preparation and Administration Precautions

Exercise caution and wear gloves when preparing gemcitabine for injection solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if gemcitabine for injection contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption. For further guidance on handling gemcitabine for injection go to "OSHA Hazardous Drugs" (refer to antineoplastic weblinks including OSHA Technical Manual) at OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

2.7 Preparation for Intravenous Infusion Administration

The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine 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, 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial or 50 mL of 0.9% Sodium Chloride Injection to the 2-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, 1.3 mL for the 1-g vial or 2.6 mL for the 2-g vial). The total volume upon reconstitution will be 5.26 mL, 26.3 mL or 52.6 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg, 1 g or 2 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 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 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 should not be refrigerated, as crystallization may occur.

No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS

Gemcitabine for injection is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg, 1 g or 2 g gemcitabine.

4 CONTRAINDICATIONS

Gemcitabine for injection is contraindicated in patients with a known hypersensitivity to gemcitabine.

5 WARNINGS AND PRECAUTIONS

5.1 Schedule-dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of gemcitabine is influenced by the length of the infusion *[see Clinical Pharmacology (12.3)]*.

5.2 Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic drugs. In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent gemcitabine. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving gemcitabine in combination with another drug.

5.3 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine. Discontinue gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity *[see Adverse Reactions (6.1 and 6.2)]*.

5.4 Hemolytic Uremic Syndrome

Hemolytic uremic syndrome to include fatalities from renal failure or the requirement for dialysis, can occur in patients treated with gemcitabine. In clinical trials, HUS was reported in 6 of 2, 429 patients (0.25%). Most fatal cases of renal failure were due to HUS *[see Adverse Reactions (6.1 and 6.2)]*. Assess renal function prior to initiation of gemcitabine for injection and periodically during treatment. Consider the diagnosis of HUS in patients who develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN) *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)]*. Permanently discontinue gemcitabine in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.

5.5 Hepatic Toxicity

Drug-induced liver injury, 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)]*. Administration of gemcitabine for injection in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency *[see Use in Specific Populations (8.7)]*. Assess hepatic function prior to initiation of gemcitabine for injection and periodically during treatment. Discontinue gemcitabine in patients that develop severe liver injury.

5.6 Embryo-fetal Toxicity

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking gemcitabine, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*

5.7 Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not indicated for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which gemcitabine was administered at a dose of 1,000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart) — Excessive toxicity has not been observed when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive gemcitabine for injection after prior radiation.

5.8 Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Discontinue gemcitabine if CLS develops during therapy.

5.9 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI) and discontinue gemcitabine for injection if PRES develops during therapy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label

- Schedule-Dependent Toxicity *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Pulmonary Toxicity and Respiratory Failure *[see Warnings and Precautions (5.3)]*
- Hemolytic Uremic Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*
- Embryo-fetal Toxicity *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1), and Nonclinical Toxicology (13.1)]*
- Exacerbation of Radiation Toxicity *[see Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.8)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.9)]*

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 clinical practice.

Single-Agent Use:

The data described below reflect exposure to gemcitabine for injection as a single agent administered at doses between 800 mg/m^2 to 1, 250 mg/m^2 over 30 minutes intravenously, once weekly, in 979 patients with a variety of malignancies. The most common (≥20%) adverse reactions of single-agent gemcitabine for injection are nausea/vomiting, anemia, increased ALT, increased AST, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema. The most common (≥5%) Grade 3 or 4 adverse reactions were neutropenia, nausea/vomiting; increased ALT, increase alkaline phosphatase, anemia, increased AST, and thrombocytopenia. Approximately 10% of the 979 patients discontinued gemcitabine for injection due to adverse reactions. Adverse reactions resulting in discontinuation of gemcitabine for injection in 2% of 979 patients were cardiovascular adverse events (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of gemcitabine for injection in less than 1% of the 979 patients were anemia, thrombocytopenia, hepatic dysfunction, renal dysfunction, nausea/vomiting, fever, rash, dyspnea, hemorrhage, infection, stomatitis, somnolence, flu-like syndrome, and edema.

Table 5 presents the incidence of adverse reactions reported in 979 patients with various malignancies receiving single-agent gemcitabine for injection across 5 clinical trials. Table 5 includes all clinical adverse reactions, reported in at least 10% of patients. A listing of clinically significant adverse reactions is provided following the table.

Table 5: Selected Per-Patient Incidence of Adverse Events in Patients Receiving

Single-Agent Gemcitabine for Injection[a]

	All Patients[b]		
	All Grades	Grade 3	Grade 4
Laboratory[c]			
Hematologic			
Anemia	68	7	1
Neutropenia	63	19	6
Thrombocytopenia	24	4	1
Hepatic			
Increased ALT	68	8	2
Increased AST	67	6	2
Increased Alkaline Phosphatase	55	7	2
Hyperbilirubinemia	13	2	<1
Renal			
Proteinuria	45	<1	0
Hematuria	35	<1	0
Increased BUN	16	0	0
Increased Creatinine	8	<1	0
Non-labortory[d]			
Nausea and Vomiting	69	13	1
Fever	41	2	0
Rash	30	<1	0
Dyspnea	23	3	<1
Diarrhea	19	1	0
Hemorrhage	17	<1	<1
Infection	16	1	<1
Alopecia	15	<1	0
Stomatitis	11	<1	0
Somnolence	11	<1	<1
Paresthesias	10	<1	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] Regardless of causality.
[d] For approximately 60% of patients, non-laboratory adverse events were graded only if assessed to be possibly drug-related.

- Transfusion requirements — Red blood cell transfusions (19%); platelet transfusions (<1%)
- Fever — Fever occurred in the absence of clinical infection and frequently in combination with other flu-like symptoms.
- Pulmonary — Dyspnea unrelated to underlying disease and sometimes accompanied by bronchospasm.
- Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%); <1% of patients. discontinued gemcitabine for injection due to edema.
- Flu-like Symptoms — Characterized by fever, asthenia, anorexia, headache, cough, chills, myalgia, asthenia insomnia, rhinitis, sweating, and/or malaise (19%); <1% of patients discontinued gemcitabine for injection due to flu-like symptoms
- Infection — Sepsis (<1%)
- Extravasation — Injection-site reactions (4%)
- Allergic — Bronchospasm (<2%); anaphylactoid reactions *[see Contraindications (4)]*.

Non-Small Cell Lung Cancer:

Table 6 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine for injection-treated patients and at a higher incidence in the gemcitabine plus cisplatin arm, reported in a randomized trial of gemcitabine plus cisplatin (n=262) administered in 28-day cycles as compared to cisplatin alone (n=260) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*.

Patients randomized to gemcitabine plus cisplatin received a median of 4 cycles of treatment and those randomized to cisplatin received a median of 2 cycles of treatment. In this trial, the requirement for dose adjustments (>90% versus 16%), discontinuation of treatment for adverse reactions (15% versus 8%), and the proportion of patients hospitalized (36% versus 23%) were all higher for patients receiving gemcitabine plus cisplatin arm compared to those receiving cisplatin alone. The incidence of febrile neutropenia (9/262 versus 2/260), sepsis (4% versus 1%), Grade 3 cardiac dysrhythmias (3% versus <1%) were all higher in the gemcitabine plus cisplatin arm compared to the cisplatin alone arm. 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.

Table 6: Per-Patient Incidence of Selected Adverse Reactions from Randomized Trial of Gemcitabine plus Cisplatin versus Single-Agent Cisplatin in Patients with NSCLC Occurring at Higher Incidence in Gemcitabine -Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)][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 Transfusions[e]	39			13		
Neutropenia	79	22	35	20	3	1
Thrombocytopenia	85	25	25	13	3	1
Platelet Transfusions[e]	21			<1		
Lymphopenia	75	25	18	51	12	5
Hepatic						
Increased Transaminases	22	2	1	10	1	0
Increased Alkaline Phosphatase	19	1	0	13	0	0
Renal						
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Elevated creatinine	38	4	<1	31	2	<1
Other Laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1
Non-laboratory[f]						
Nausea	93	25	2	87	20	<1
Vomiting	78	11	12	71	10	9
Alopecia	53	1	0	33	0	0
Neuro Motor	35	12	0	15	3	0
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
Hypotension	12	1	0	7	1	0
Rash	11	0	0	3	0	0

[a] National Cancer Institute Common Toxicity Criteria (CTC) for severity grading.
[b] N=217 to 253; all gemcitabine plus cisplatin patients with laboratory or non-laboratory data gemcitabine at 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at 100 mg/m^2 on Day 1 every 28 days.
[c] N=213 to 248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1every 28 days.
[d] Regardless of causality.
[e] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.
[f] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 7 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine treated patients and at a higher incidence in the gemcitabine plus cisplatin arm, reported in a randomized trial of gemcitabine plus cisplatin (n=69) administered in 21-day cycles as compared to etoposide plus cisplatin alone (n=66) in patients receiving first-line treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC) *[see Clinical Studies (14.3)]*. A listing of clinically significant adverse reactions is provided following the table.

Patients in the gemcitabine cisplatin (GC) arm received a median of 5 cycles and those in the etoposide/cisplatin (EC) arm received a median of 4 cycles. The majority of patients receiving more than one cycle of treatment required dose adjustments; 81% in the (GC) arm and 68% in the (EC) arm. The incidence of hospitalizations for treatment-related adverse events was 22% (GC) and 27% in the (EC) arm. The proportion of discontinuation of treatment for treatment-related adverse reactions was higher for patients in the (GC) arm (14% versus 8%). The proportion of patients hospitalized for febrile neutropenia was lower in the (GC) arm (7% versus 12%). There was one death attributed to treatment, a patient with febrile neutropenia and renal failure, which occurred in the gemcitabine /cisplatin arm.

Table 7: Per-Patient Incidence of Selected Adverse Reactions in Randomized Trial of Gemcitabine plus Cisplatin versus Etoposide plus Cisplatin in Patients with NSCLC[a]

	Gemcitabine plus Cisplatin[b]			Etoposide plus Cisplatin[c]		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[d]						
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusions[e]	29	-	-	21	-	-
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet Transfusions[e]	3	-	-	8	-	-
Hepatic						
Increased ALT	6	0	0	12	0	0
Increased AST	3	0	0	11	0	0
Increased 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[f]						
Nausea and Vomiting	96	35	4	86	19	7
Fever	6	0	0	3	0	0
Rash	10	0	0	3	0	0
Dyspnea	1	0	1	3	0	0
Diarrhea	14	1	1	13	0	2
Hemorrhage	9	0	3	3	0	3
Infection	28	3	1	21	8	0
Alopecia	77	13	0	92	51	0
Stomatitis	20	4	0	18	2	0
Somnolence	3	0	0	3	2	0
Paresthesias	38	0	0	16	2	0
Flu-like syndrome[g]	3	-	-	0	-	-
Edemag	12	-	-	2	-	-

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=67 to 69; all gemcitabine plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine at 1,250 mg/m2 on Days 1 and 8 and cisplatin at 100 mg/m2 on Day 1 every 21 days.
[c] N=57 to 63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m2 on Day 1 and intravenous etoposide at 100 mg/m2 on Days 1, 2, and 3 every 21 days.
[d] Regardless of causality.
[e] WHO grading scale not applicable to proportion of patients with transfusions
[f] Non-laboratory events were graded only if assessed to be possibly drug-related. Pain data were not collected.
[g] Flu-like syndrome and edema were not graded.

Breast Cancer

Table 8 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine treated patients and at a higher incidence in the gemcitabine plus paclitaxel arm, reported in a randomized trial of gemcitabine plus paclitaxel (n=262) compared to paclitaxel alone (n=259) for the first-line treatment of metastatic breast cancer (MBC) in women who received anthracycline-containing chemotherapy in the adjuvant/neo-adjuvant setting or for whom anthracyclines were contraindicated. *[see Clinical Studies (14.2)]*.

The requirement for dose reduction of paclitaxel were higher for patients in the gemcitabine/paclitaxel arm (5% versus 2%). The number of paclitaxel doses omitted (<1%), the proportion of patients discontinuing treatment for treatment-related adverse reactions (7% versus 5%), and the number of treatment-related deaths (1 patient in each arm) were similar between the two arms.

Table 8: Per-Patient Incidence of Selected Adverse Reactions from Comparative Trial of Gemcitabine plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer[a] Occurring at Higher Incidence in Gemcitabine-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	Gemcitabine plus Paclitaxel (N=262)			Paclitaxel (N=259)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory[b]						
Hematologic						
Anemia	69	6	1	51	3	<1
Neutropenia	69	31	17	31	4	7
Thrombocytopenia	26	5	<1	7	<1	<1
Hepatobiliary						
Increased ALT	18	5	<1	6	<1	0
Increased AST	16	2	0	5	<1	0
Non-laboratory[c]						
Alopecia	90	14	4	92	19	3
Neuropathy-sensory	64	5	<1	58	3	0
Nausea	50	1	0	31	2	0
Fatigue	40	6	<1	28	1	<1
Vomiting	29	2	0	15	2	0
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
Rash/desquamation	11	<1	<1	5	0	0
Febrile neutropenia	6	5	<1	2	1	0

[a] Severity grade based on National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0
[b] Regardless of Causality.
[C] Non-laboratory events were graded only if assessed to be possibly drug-related.

Clinically relevant Grade 3 or 4 dyspnea occurred with a higher incidence in the gemcitabine plus paclitaxel arm compared with the paclitaxel arm (1.9% versus 0).

Ovarian Cancer

Table 9 presents the incidence of selected adverse reactions, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the gemcitabine plus carboplatin arm, reported in a randomized trial of gemcitabine plus carboplatin (n=175) compared to carboplatin alone (n=174) for the second-line treatment of ovarian cancer in women with disease that had relapsed more than 6 months following first-line platinum-based chemotherapy. *[see Clinical Studies (14.1)]*. Additional clinically significant adverse reactions, occurring in less than 10% of patients, are provided following Table 9.

The proportion of patients with dose adjustments for carboplatin (1.8% versus 3.8%), doses of carboplatin omitted (0.2% versus 0), and discontinuing treatment for treatment-related adverse reactions (10.9% versus 9.8%), were similar between arms. Dose adjustment for gemcitabine occurred in 10.4% of patients and gemcitabine dose was omitted in 13.7% of patients in the gemcitabine/carboplatin arm.

Table 9: Per-Patient Incidence of Adverse Reactions in Randomized Trial of Gemcitabine plus Carboplatin versus Carboplatin in Ovarian Cancer[a] Occurring at Higher Incidence in gemcitabine-treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

	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
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
Diarrhea	25	3	0	14	<1	0
Stomatitis/ pharyngitis	22	<1	0	13	0	0

[a] Grade based on Common Toxicity Criteria (CTC) Version 2.0.
[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.

Hematopoietic growth factors were administered more frequently in the gemcitabine-containing arm: granulocyte growth factors (23.6% and 10.1%) and erythropoietic agents (7.3% and 3.9%).

The following clinically relevant, Grade 3 and 4 adverse reactions occurred more frequently in the gemcitabine plus carboplatin arm: dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1 %), motor neuropathy (1.1% versus 0.6%), and rash/ desquamation (0.6% versus 0).

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.

Cardiovascular — Congestive heart failure, myocardial infarction, arrhythmias, supraventricular arrhythmias

Vascular Disorders — Peripheral vasculitis, gangrene, and capillary leak syndrome *[see Warnings and Precautions (5.8)]*

Skin — Cellulitis, severe skin reactions, including desquamation and bullous skin eruptions

Hepatic — Hepatic failure, hepatic veno-occlusive disease

Pulmonary — Interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS)

Nervous System — Posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.9)]*

7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.6)]*

Risk Summary

Gemcitabine 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. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. 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 a fetus.

Animal Data

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (approximately 0.005 times 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 0.002 times the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays [*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, 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 have not been established in pediatric patients. The safety and pharmacokinetics of gemcitabine were evaluated in a trial in pediatric patients with refractory leukemia. The maximum tolerated dose was 10 mg/m^2/min for 360 minutes three times weekly followed by a one week rest period. The safety and activity of gemcitabine were evaluated in a trial of pediatric patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) at a dose of 10 mg/m^2/min administered over 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. No meaningful clinical activity was observed in this trial.

8.5 Geriatric Use

In clinical studies of gemcitabine, enrolling 979 patients with various cancers who received gemcitabine for injection as a single agent, no overall differences in safety were observed between patients aged 65 and older and younger patients, with the exception of a higher rate of Grade 3-4 thrombocytopenia in older patients as compared to younger patients. In a randomized trial in women with ovarian cancer, 175 women received gemcitabine plus carboplatin, of which 29% were age 65 years or older. 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.

Gemcitabine clearance is affected by age, however there are no recommended dose adjustments based on patients' age *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased renal function.

8.7 Hepatic Impairment

No clinical studies have been conducted with gemcitabine in patients with decreased hepatic function.

8.8 Gender

Gemcitabine clearance is affected by gender *[see Clinical Pharmacology (12.3)]*. In single-agent studies of gemcitabine, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

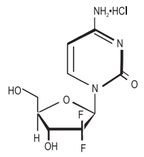
10 OVERDOSAGE

Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5,700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a dose-escalation study.

11 DESCRIPTION

Gemcitabine for injection, USP is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



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

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 supplied in a sterile form for intravenous use only. Vials of gemcitabine contain either 200 mg, 1 g or 2 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg, 1 g or 2 g, respectively) and sodium acetate (12.5 mg, 62.5 mg, or 125 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. 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, which eventually results in the initiation of apoptotic cell death.

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 for injection dose varied from 500 to 3,600 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 1,000 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.

Elimination

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 10 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 10: 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	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving <70 minute infusion.

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 (1,250 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. Analysis of data from metastatic breast cancer patients shows that, on average, gemcitabine for injection 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 for injection have not been conducted. Gemcitabine was mutagenic in an *in vitro* mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. 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 1/1,300 the human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

The safety and efficacy of gemcitabine was studied in a randomized trial of 356 women with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either gemcitabine 1,000 mg/m^2 on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after gemcitabine infusion on Day 1 of each cycle (n=178) or to carboplatin AUC 5 administered on Day 1 of each 21-day cycle (n=178). The primary efficacy outcome measure was progression free survival (PFS).

Patient characteristics are shown in Table 11. The addition of gemcitabine to carboplatin resulted in statistically significant improvements in PFS and overall response rate as shown in Table 12 and Figure 1. Approximately 75% of patients in each arm received additional chemotherapy for disease progression; 13 of 120 patients in the carboplatin alone arm received gemcitabine for treatment of disease progression. There was no significant difference in overall survival between the treatment arms.

Table 11: Randomized Trial of 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 0-1[a]	94%	95%
Disease Status Evaluable Bidimensionally measurable	 8% 92%	 3% 96%
Platinum-free interval[b] 6 to 12 months >12 months	 40% 59%	 40% 60%
First-line therapy Platinum-taxane combination Platinum-non-taxane combination Platinum monotherapy	 70% 29% 1%	 71% 28% 1%

[a] 5 patients on Gemcitabine plus carboplatin arm and 4 patients on carboplatin arm with no baseline Eastern Cooperative Oncology Group (ECOG) performance status.
[b] 2 on Gemcitabine plus carboplatin arm and 1 on carboplatin arm had platinum-free interval <6 months.

Table 12: Randomized Trial of Gemcitabine plus Carboplatin versus Carboplatin in Ovarian Cancer - Efficacy Outcomes

	Gemcitabine/Carboplatin (N=178)	Carboplatin (N=178)
Progression-free Survival Median (95% CI[a]) months Hazard Ratio (95% CI)	8.6 (8, 9.7) 0.72 (0.57, 0.90)	5.8 (5.2, 7.1)
p-value[b]	p=0.0038	
Overall Survival Median (95% CI) months Hazard Ratio (95% CI)	18 (16.2, 20.3) 0.98 (0.78, 1.24)	17.3 (15.2, 19.3)
p-value[b]	p=0.8977	
Investigator Reviewed Overall Response Rate	47.2%	30.9%
p-value[c]	p=0.0016	
CR[d] PR plus PRNM[e]	14.6% 32.6%	6.2% 24.7%
Independently Reviewed Overall Response Rate[f]		
p-value[c]	p=0.11	
CR[d] PR plus PRNM[e]	9.1% 37.2%	4.0% 31.7%

[a] CI=confidence interval.
[b] Log rank, unadjusted.
[c] Chi square.
[d] CR=Complete response.
[e] PR plus PRNM=Partial response plus partial response, non-measurable disease.
[f] Independently reviewed cohort - gemcitabine/carboplatin (n=121), carboplatin (n=101); independent reviewers unable to measure disease detected by sonography or physical exam.

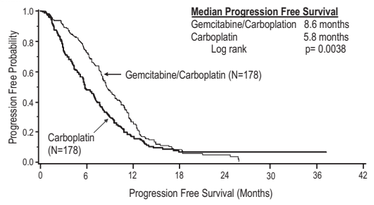


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemcitabine plus Carboplatin versus Carboplatin

14.2 Breast Cancer

The safety and efficacy of gemcitabine were evaluated in a multi-national, randomized, open-label trial conducted in women receiving initial treatment for metastatic breast cancer in women who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Patients were randomized to receive gemcitabine for injection 1,250 mg/m^2 on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m^2 administered prior to gemcitabine for injection on Day 1 of each cycle (n=267) or to receive paclitaxel 175 mg/m^2 was administered on Day 1 of each 21-day cycle (n=262). The primary efficacy outcome measure was time to documented disease progression.

A total of 529 patients were enrolled; 267 were randomized to gemcitabine and paclitaxel and 262 to paclitaxel alone. Demographic and baseline characteristics were similar between treatment arms (see Table 13). Efficacy results are presented in Table 13 and Figure 2. The addition of gemcitabine to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to paclitaxel alone. There was no significant difference in overall survival.

Table 13: Randomized Trial of Gemcitabine plus Paclitaxel versus Paclitaxel in Breast Cancer

	Gemcitabine/ Paclitaxel	Paclitaxel
Number of patients	267	262
Demographic/Entry Characteristics Median age (years) Range	 53 26 to 83	 52 26 to 75
Metastatic disease	97%	97%
Baseline KPS[a] ≥90	70%	74%
Number of tumor sites 1 to 2 ≥3	 57% 43%	 59% 41%
Visceral disease	73%	73%
Prior anthracycline	97%	96%
Efficacy Outcomes		
Time to Documented Disease Progression[b]		
Median in months (95% CI)	5.2 (4.2, 5.6)	2.9 (2.6, 3.7)
Hazard Ratio (95% CI)	0.650 (0.524, 0.805)	
p-value	p<0.0001	
Overall Survival[c]		
Median Survival in months (95% CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)
Hazard Ratio (95% CI)	0.86 (0.71, 1.04)	
p-value	Not Significant	
Overall Response Rate (95% CI)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)
p-value	p<0.0001	

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

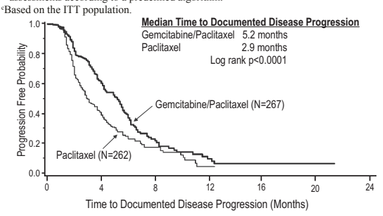


Figure 2: Kaplan-Meier Curve of Time to Documented Disease Progression in Gemcitabine Plus Paclitaxel Versus Paclitaxel Breast Cancer Study (N=529)

14.3 Non-Small Cell Lung Cancer (NSCLC)

The safety and efficacy of gemcitabine was evaluated in two randomized, multicenter trials.

28-Day Schedule

A multinational, randomized trial compared gemcitabine plus cisplatin to cisplatin alone in the treatment of patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Patients were randomized to receive gemcitabine for injection 1,000 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 administered on Day 1 of each cycle or to receive cisplatin 100 mg/m^2 on Day 1 of each 28-day cycle. The primary efficacy outcome measure was overall survival. A total of 522 patients were enrolled at clinical centers in Europe, the US, and Canada. Patient demographics and baseline characteristics (shown in Table 14) were similar between arms with the exception of histologic subtype of NSCLC, with 48% of patients on the cisplatin arm and 37% of patients on the gemcitabine plus cisplatin arm having adenocarcinoma. Efficacy results are presented in Table 14 and Figure 3 for overall survival.

21-Day Schedule

A randomized (1:1), multicenter trial was conducted in 135 patients with Stage IIIB or IV NSCLC. Patients were randomized to receive gemcitabine for injection 1,250 mg/m^2 on Days 1 and 8, and cisplatin 100 mg/m^2 on Day 1 of a 21-day cycle or to receive etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 and cisplatin 100 mg/m^2 on Day 1 of a 21 -day cycle.

There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two sided, see Table 14). The median survival was 8.7 months for the gemcitabine plus cisplatin arm versus 7months for the etoposide plus cisplatin arm. Median time to disease progression for the gemcitabine plus cisplatin arm was 5 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).

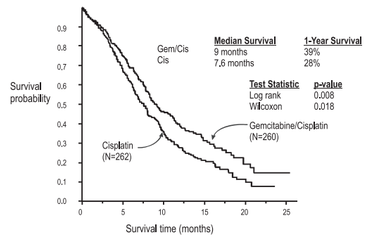


Figure 3: Kaplan-Meier Survival Curve in Gemcitabine plus Cisplatin versus Cisplatin in Patients with NSCLC Study (N=522).

Table 14: Randomized Trials of Gemcitabine plus Cisplatin in Patients with NSCLC

Trial	28-day Schedule[a]		21-day Schedule[b]	
Treatment Arm	Gemcitabine plus Cisplatin	Cisplatin	Gemcitabine plus Cisplatin	Etoposide plus Cisplatin
Number of patients	260	262	69	66
Demographic/Entry Characteristics				
Male	70%	71%	93%	92%
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[c]	N/A[c]
Stage IIIB	26%	23%	48%	52%
Stage IV	67%	70%	52%	49%
Baseline KPS[d] 70 to 80	41%	44%	45%	52%
Baseline KPS[d] 90 to100	57%	55%	55%	49%
Efficacy Outcomes				
Survival				
Median in months	9	7.6	8.7	7.0
(95% CI[e]) months	8.2, 11	6.6, 8.8	7.8, 10.1	6.0, 9.7
p-value[f]	p=0.008		p=0.18	
Time to Disease Progression				
Median in months	5.2	3.7	5.0	4.1
(95% CI[e]) months	4.2, 5.7	3, 4.3	4.2, 6.4	2.4, 4.5
p-value[f]	p=0.009		p=0.015	
Tumor Response	26%	10%	33%	14%
p-value[f]	p<0.0001		p=0.01	

[a] 28-day schedule — Gemcitabine plus cisplatin: Gemcitabine 1,000 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 1,250 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] CI=confidence intervals.
[f] p-value two-sided Fisher's Exact test for difference in binomial proportions; log rank test for time-to-event analyses.

14.4 Pancreatic Cancer

The safety and efficacy of gemcitabine for injection was evaluated in two trials, a randomized, single-blind, two-arm, active-controlled trial conducted in patients with locally advanced or metastatic pancreatic cancer who had received no prior chemotherapy and in a single-arm, open-label, multicenter trial conducted in patients with locally advanced or metastatic pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The first trial randomized patients to receive gemcitabine for injection 1,000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles (n=63) or to 5-fluorouracil (5-FU) 600 mg/m^2 intravenously over 30 minutes once weekly (n=63). In the second trial, all patients received gemcitabine for injection 1,000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly dosing for 3 consecutive weeks every 28-days in subsequent cycles.

The primary efficacy outcome measure in both trials was "clinical benefit response". A patient was considered to have had a clinical benefit response if either of the following occurred:

- The patient achieved 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

- 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 randomized trial enrolled 126 patients across 17 sites in the US and Canada. The demographic and entry characteristics were similar between the arms (Table 15). The efficacy outcome results are shown in Table 15 and for overall survival in Figure 4. Patients treated with gemcitabine for injection had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to those randomized to receive 5-FU. No confirmed objective tumor responses were observed in either treatment arm.

Table 15: Randomized Trial of Gemcitabine versus 5-Fluorouracil in Pancreatic Cancer

	Gemcitabine	5-FU
Number of patients	63	63
Demographic/Entry Characteristics	54%	54%
Male	62 years	61 years
Median age		
Range	37 to 79	36 to 77
Stage IV disease	71%	76%
Baseline KPS[a] ≤70	70%	68%
Efficacy Outcomes		
Clinical benefit response	22.2%	4.8%
p-value[b]	p=0.004	
Survival		
Median	5.7 months	4.2 months
(95% CI)	(4.7, 6.9)	(3.1, 5.1)
p-value[b]	p=0.0009	
Time to Disease Progression		
Median	2.1 months	0.9 months
(95% CI)	(1.9, 3.4)	(0.9, 1.1)
p-value[b]	p=0.0013	

[a] Karnofsky Performance Status.
[b] p-value for clinical benefit response calculated using the two-sided test for difference in binomial proportions. All other p-values are calculated using log rank test.

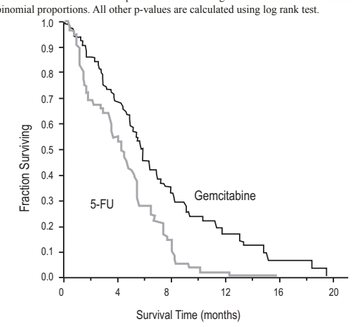


Figure 4: Kaplan-Meier Survival Curve.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemcitabine for Injection, USP is supplied as a sterile, lyophilized powder as follows:

Product No.	NDC No.	Strength	
FK101210	63323-102-13	200 mg per vial	10 mL single use vial packaged individually.
FK102550	63323-125-53	1 g per vial	50 mL single use vial packaged individually.
FK102600	63323-126-03	2 g per vial	100 mL single use vial packaged individually.

16.2 Storage and Handling

Unopened vials of gemcitabine for injection, USP are stable until the expiration date indicated on the package when stored at controlled room temperature 20º to 25ºC (68º to 77ºF) and that allows for excursions between 15º and 30ºC (59º and 86ºF) [see USP Controlled Room Temperature] *[see Dosage and Administration (2.6 and 2.7)]*.

This container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

- Advise patients of the risks of low blood cell counts and the potential need for blood transfusions and increased susceptibility to infections. Instruct patients to immediately contact their healthcare provided for development of signs or symptoms of infection, fever, prolonged or unexpected bleeding, bruising, or shortness of breath *[see Warnings and Precautions (5.2)]*.
- Advise patients of the risks of pulmonary toxicity including respiratory failure and death. Instruct patients to immediately contact their healthcare provider for development of shortness of breath, wheezing, or cough *[see Warnings and Precautions (5.3)]*.
- Advise patients of the risks of hemolytic-uremic syndrome and associated renal failure. Instruct patients to immediately contact their healthcare provider for changes in the color or volume of urine output or for increased bruising or bleeding *[see Warnings and Precautions (5.4)]*.
- Advise patients of the risks of hepatic toxicity including liver failure and death. Instruct patients to immediately contact their healthcare provider for signs of jaundice or for pain/tenderness in the right upper abdominal quadrant *[see Warnings and Precautions (5.5)]*.

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