HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GEMCITABINE INJECTION safely and effectively. See full prescribing information for GEMCITABINE INJECTION.

GEMCITABINE injection, for intravenous use
Initial U.S. Approval: 1996

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

Gemcitabine Injection 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 Injection is for intravenous infusion 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: 1000 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: 1000 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----------

Gemcitabine Injection in multiple dose vials containing:

- 200 mg/2 mL (100 mg/mL) (3)
- 1 g/10 mL (100 mg/mL) (3)
- 1.5 g/15 mL (100 mg/mL) (3)
- 2 g/20 mL (100 mg/mL) (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 Injection 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 Injection for HUS or severe renal impairment. (5.4)
- Hepatoxicity: Monitor hepatic function prior to initiation and during therapy. Discontinue Gemcitabine Injection for severe hepatic toxicity. (5.5)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females and males of reproductive potential to use of effective contraception. (5.6, 8.1, 8.3)
- Exacerbation of radiationtherapy 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 Injection. (5.8)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue Gemcitabine Injection. (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 Accord Healthcare Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2018

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 Injection 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 Injection 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 Injection 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 Injection 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 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 Injection is 1000 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 Injection administration on Day 1 of each 21-day cycle. Refer to the carboplatin prescribing information for additional information.

Dose Modifications

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

Table 1: Dose Modification Guidelines for Gemcitabine Injection for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	Absolute neutrophil count ($\times 10^6$/L)		Platelet count ($\times 10^6$/L)	Dose modification
Day 1	≥ to 1500	and	≥ to 100,000	None
	< 1500	or	< 100,000	Delay Treatment Cycle
Day 8	≥ to 1500	and	≥ to 100,000	None
	1000-1499	or	75,000-99,999	50% of full dose
	< 1000	or	< 75,000	Hold

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

Occurrence	Myelosuppression During Treatment Cycle	Dose Modification
Initial Occurrence	Absolute neutrophil 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 < 25,000x10^6/L Cycle delay of more than one week due to toxicity	Permanently reduce Gemcitabine Injection 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 Injection dose to 800 mg/m^2 on Day 1 only

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of Gemcitabine Injection is 1250 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 Injection administration. Refer to the paclitaxel prescribing information for additional information.

Dose Modifications

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

Table 3: Recommended Dose Modifications for Myelosuppression on Day of Treatment in Breast Cancer

Treatment Day	Absolute neutrophil count (x 10^6/L)		Platelet count (x 10^6/L)	Dose modification
Day 1	≥ to 1500	and	≥ to 100,000	None
	< 1500	or	<100,000	Hold
Day 8	≥ to 1200	and	> 75,000	None
	1000-1199	or	50,000-75,000	75% of full dose
	700-999	and	≥ to 50,000	50% of full dose
	< 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 Injection is 1000 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 Injection.

Every 3-week schedule

The recommended dose of Gemcitabine Injection is 1250 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 Injection.

Refer to the cisplatin prescribing information for additional information.

Dose Modifications
Table 4 presents the recommended dose modifications for Gemcitabine Injection myelosuppression *[see Warnings and Precautions (5.2)]*. Refer to the dose modification recommendations for non-hematologic adverse reactions *[see Dosage and Administration (2.5)]*.

2.4 Pancreatic Cancer

Recommended Dose and Schedule
The recommended dose of Gemcitabine Injection is 1000 mg/m^2 over 30 minutes intravenously. The recommended treatment schedule is as follows:

- Weeks 1-8: 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
Table 4 presents the recommended dose modifications for Gemcitabine Injection for myelosuppression *[see Warnings and Precautions (5.2)]*. Refer to the dose modification recommendations for non-hematologic adverse reactions *[see Dosage and Administration (2.5)]*.

If myelosuppression is detected, therapy should be modified or suspended according to the guidelines in Table 4.

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

Absolute neutrophil count ($\times 10^6$/L)		**Platelet count ($\times 10^6$/L)**	**Dose modification**
≥ to 1000	and	≥ to 100,000	None
500-999	or	50,000-99,999	75% of full dose
< 500	or	< 50,000	Hold

2.5 Dose Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemcitabine Injection for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity *[see Warnings and Precautions (5.3)]*
- Severe hepatic toxicity *[see Warnings and Precautions (5.5)]*
- Hemolytic-uremic syndrome *[see Warnings and Precautions (5.4)]*
- Capillary leak syndrome *[see Warnings and Precautions (5.8)]*
- Posterior reversible encephalopathy syndrome *[see Warnings and Precautions (5.9)]*

Withhold Gemcitabine Injection or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved.

2.6 Preparation and Administration

Gemcitabine Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Exercise caution and wear gloves when preparing Gemcitabine Injection solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemcitabine Injection contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.

Preparation

- Inspect solution and discard vial if particulate matter or discoloration is observed.
- Dilute Gemcitabine Injection with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.

After dilution with 0.9% Sodium Chloride Injection, inspect the solution visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

Storage

- After initial withdrawal with a needle, the remaining portion in the vial should be used or discarded within 28 days.
- Store diluted Gemcitabine Injection at controlled room temperature 20°C to 25°C (68°F to 77°F) Discard after 24 hours.

Administration

- Inspect the infusion solution for particulate matter and discoloration prior to administration. If particulate matter or discoloration is found, do not administer.
- The compatibility of Gemcitabine Injection 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 Injection is a clear, colorless to pale yellow solution available in sterile multiple-dose vials containing

- 200 mg/2 mL (100 mg/mL)
- 1 g/10 mL (100 mg/mL)
- 1.5 g/15 mL (100 mg/mL)
- 2 g/ 20 mL (100 mg/mL)

4 CONTRAINDICATIONS

Gemcitabine Injection is contraindicated in patients with a known hypersensitivity to gemcitabine. *[see Adverse Reactions (6.1)]*.

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)]*. [Refer to the recommended Gemcitabine Injection dosing schedule *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.]

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 *[see Adverse Reactions (6.1)]*. Monitor patients receiving Gemcitabine Injection prior to each dose with a complete blood count (CBC), including differential and platelet count and modify the dose as recommended *[see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)]*.

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.

Permanently discontinue Gemcitabine Injection in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity *[see Dosage and Administration (2.5) and Adverse Reactions (6.1 and 6.2)]*.

5.4 Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS), including 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 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS *[see Adverse Reactions (6.1)]*.

Assess renal function prior to initiation of Gemcitabine Injection and periodically during treatment. Consider the diagnosis of HUS in patients who develop 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)]*. Permanently discontinue Gemcitabine Injection 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 hepatic injury, including hepatic 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 in patients with concurrent hepatic metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.

Assess hepatic function prior to initiation of Gemcitabine Injection and periodically during treatment. Permanently discontinue Gemcitabine Injection 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. Advise pregnant women of the potential risk to a fetus. *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with Gemcitabine Injection and for 6 months after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during and for 3 months following the final dose of Gemcitabine Injection *[see Use in Specific Populations (8.1) and (8.3)]*.

5.7 Exacerbation of Radiation Therapy Toxicity

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

Concurrent (given together or less or equal than 7 days apart) — Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which gemcitabine was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given more than 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 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. Permanently discontinue Gemcitabine Injection 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. Patients 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 permanently discontinue Gemcitabine 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

- Hypersensitivity *[see Contraindications (4)]*
- 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)]*
- 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 as a single agent administered at doses between 800 mg/m^2 to 1250 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 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 due to adverse reactions. Adverse reactions resulting in discontinuation of gemcitabine in 2% of 979 patients were cardiovascular adverse reactions (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of gemcitabine 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 across 5 clinical trials. Listings of clinically significant adverse reactions and laboratory abnormalities are provided in tables 5 and 6.

Table 5: Per-Patient Incidence of Selected Adverse Reactions in Patients Receiving Single-Agent Gemcitabine[a]

Adverse Reactions [c]	All Patients[b]		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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=699-974
[c] For approximately 60% of patients, non-laboratory adverse reactions were graded only if assessed to be possibly drug-related.

Table 6 includes incidences of laboratory abnormalities in patients receiving gemcitabine as a single-agent administered at doses between 800 mg/m^2 to 1250 mg/m^2 across 5 clinical trials.

Table 6: Per-Patient Selected Laboratory Abnormalities in Patients Receiving Single-Agent Gemcitabine[a]

Laboratory Abnormality [c]	All Patients[b]		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=699-974
[c] Regardless of causality.

- Transfusion requirements — red blood cell transfusions (19%); platelet transfusions (<1%)
- Edema — edema (13%), peripheral edema (20%), and generalized edema (<1%);
- Flu-like Symptoms — fever, asthenia, anorexia, headache, cough, chills, myalgia, asthenia insomnia, rhinitis, sweating, and/or malaise (19%);
- Infection — sepsis (<1%)
- Extravasation — injection-site reactions (4%)
- Allergic — bronchospasm (<2%); anaphylactoid reactions).

Non-Small Cell Lung Cancer:

Table 7 and 8 present the incidence of 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 (Study 3) of gemcitabine plus cisplatin (n=262) with gemcitabine at dose 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin at dose 100 mg/m^2 on Day 1 administered every 28-day cycle 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 7: 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]		
Non-laboratory[d]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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=217-253; all gemcitabine plus cisplatin patients with 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=213-248; all cisplatin patients with non-laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

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

Table 8: Per-Patient Incidence of Selected Laboratory Abnormalities 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]		
Laboratory Abnormalities[d]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	89	22	3	67	6	1
Thrombocytopenia	85	25	25	13	3	1
Neutropenia	79	22	35	20	3	1
Lymphopenia	75	25	18	51	12	5
RBC transfusion[e]	39			13		
Platelet transfusions[e]	21			<1		
Hepatic						
Increased transaminases	22	2	1	10	1	0
Increased alkaline Phosphatase	19	1	0	13	0	0
Renal						
Elevated creatinine	38	4	<1	31	2	<1
Proteinuria	23	0	0	18	0	0
Hematuria	15	0	0	13	0	0
Other laboratory						
Hyperglycemia	30	4	0	23	3	0
Hypomagnesemia	30	4	3	17	2	0
Hypocalcemia	18	2	0	7	0	<1

[a] National Cancer Institute Common Toxicity Criteria (CTC) for severity grading.

[b] N=217-253; all gemcitabine plus cisplatin patients with 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=213-248; all cisplatin patients with laboratory data. Cisplatin at 100 mg/m^2 on Day 1 every 28 days.

[d] Regardless of causality.

[e] Percent of patients receiving transfusions.

Table 9 presents the incidence of 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 (Study 4) of gemcitabine plus cisplatin (n=69) with gemcitabine at dose 1250 mg/m^2 on Days 1, and 8 and cisplatin at dose 100 mg/m^2 on Day 1 administered every 21-day cycle administered in 21-day cycles as compared to etoposide plus cisplatin alone (n=66) with etoposide at dose 100 mg/m^2 on Days 1, 2 and 3 and cisplatin at dose 100 mg/m^2 on Day 1 administered every 21-day cycle 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 plus cisplatin (GC) arm received a median of 5 cycles and those in the etoposide plus-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 reactions 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 9: 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]		
Non-laboratory [d]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Nausea and Vomiting	96	35	4	86	19	7
Alopecia	77	13	0	92	51	0
Paresthesias	38	0	0	16	2	0
Infection	28	3	1	21	8	0
Stomatitis	20	4	0	18	2	0
Diarrhea	14	1	1	13	0	2
Edema[g]	12	-	-	2	-	-
Rash	10	0	0	3	0	0
Hemorrhage	9	0	3	3	0	3
Fever	6	0	0	3	0	0
Flu-like syndrome [e]	3	-	-	0	-	-
Somnolence	3	0	0	3	2	0
Dyspnea	1	0	1	3	0	0

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=67-69; all gemcitabine plus cisplatin patients with non-laboratory data. Gemcitabine at 1250mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.
[c] N=57-63; all cisplatin plus etoposide patients with non-laboratory data. Cisplatin at 100mg/m^2 on Day 1 and intravenous etoposide at 100mg/m^2 on Days 1, 2, and 3 every 21 days.
[d] Non-laboratory events were graded only if assessed to be possibly drug-related.
[e] Flu-like syndrome and edema were not graded.

Table 10: Per-Patient Incidence of Selected Laboratory Abnormalities in Randomized Trial of Gemcitabine plus Cisplatin versus Etoposide plus Cisplatin in Patients with NSCLC[a]

	Gemcitabine plus Cisplatin [b]			Etoposide plus Cisplatin [c]		
Laboratory Abnormalities [d]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	88	22	0	77	13	2
RBC Transfusionse	29	-	-	21	-	-
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
Platelet transfusionse	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

[a] Grade based on criteria from the World Health Organization (WHO).
[b] N=67-69; all gemcitabine plus cisplatin patients with non-laboratory data. Gemcitabine at 1250mg/m^2 on Days 1 and 8 and cisplatin at 100 mg/m^2 on Day 1 every 21 days.
[c] N=57-63; all cisplatin plus etoposide patients with non-laboratory data. Cisplatin at 100mg/m^2 on Day 1 and intravenous etoposide at 100mg/m^2 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.

Metastatic Breast Cancer

Table 11 and 12 present 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 Study 2, 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 11: Per-Patient Incidence of Selected Adverse Reactions[a] from Comparative Trial of Gemcitabine plus Paclitaxel versus single-Agent Paclitaxel in Breast Cancer 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		
Non-laboratory [b]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 12: Per-Patient Incidence of Selected Laboratory Abnormalities[a] from Comparative Trial of Gemzar plus Paclitaxel versus Single-Agent Paclitaxel in Breast Cancer 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		
Laboratory Abnormalities[b]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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

[a] Severity grade based on National Cancer Institute Common Toxicity Criteria (CTC) Version 2.0.
[b] Regardless of causality.

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 13 and 14 present 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 13.

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 plus carboplatin arm.

Table 13: Per-Patient Incidence of Adverse Reactions[a] in Randomized Trial of Gemcitabine plus Carboplatin versus Carboplatin in Ovarian Cancer 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		
Non-laboratory[b]	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
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 National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 2.0.
[b] Regardless of causality.

Table 14: Per-Patient Incidence of Laboratory Abnormalities[a] in Randomized Trial of Gemcitabine plus Carboplatin versus Carboplatin in Ovarian Cancer Occurring at Higher Incidence in Gemcitabine-Treated Patients [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)]

Laboratory Abnormalities[b]	Gemcitabine plus Carboplatin N=175			Carboplatin N=174		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
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		

[a] Grade based on National Cancer Institute Common Toxicity Criteria (NCI 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

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)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine Injection is expected to result in adverse reproductive effects. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. Advise pregnant women of the potential risk to a fetus [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

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.

8.2 Lactation

Risk Summary

There are no data on the presence of gemcitabine in human milk, or the effects of gemcitabine on the breastfed infant or milk production. Because of the potential for serious adverse reactions in nursing infants from Gemcitabine Injection, advise a lactating woman not to breastfeed during treatment with Gemcitabine Injection and for one week after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Gemcitabine Injection and for 6 months after the final dose *[see Use in Specific Populations (8.1)]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 3 months following the final dose of Gemcitabine Injection *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on animal studies, Gemcitabine Injection may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Gemcitabine Injection 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 weekly for three weeks 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 weekly for three weeks followed by a one-week rest period. Patients with M1 or M2 bone marrow on Day 28 who did not experience unacceptable toxicity were eligible to receive a maximum of one additional four-week course. Toxicities observed included myelosuppression, 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 as a single agent, no overall differences in safety were observed between patients aged 65 and older and younger patients, except for a higher rate of Grade 3-4 thrombocytopenia in older patients 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 however, a significantly higher incidence of Grade 3/4 neutropenia in women 65 years of age or older was observed *[see Dosage and Administration (2.1-2.4)]*.

8.6 Gender

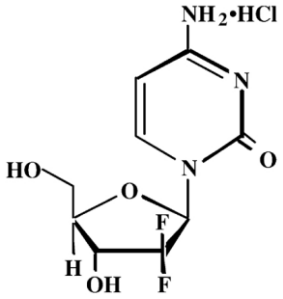
Gemcitabine clearance is decreased in females *[see Clinical Pharmacology (12.3)]*. In single-agent studies of gemcitabine, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia *[see Dosage and Administration (2.1-2.4)]*.

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 dose-escalation 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 is a nucleoside metabolic inhibitor. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).
The structural formula is



Gemcitabine HCl is a white to off white crystalline powder. The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl and the molecular weight is 299.66.
Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine Injection is supplied as a sterile, clear colorless to pale yellow solution in multiple-dose vials for intravenous use only. Vials of Gemcitabine Injection are available in four presentations: 200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL or 2 g/20 mL. Each mL contains 100 mg of gemcitabine free base (equivalent to 113.85 mg of gemcitabine HCl), 250 mg PEG-300, 150 mg propylene glycol, and 16 mg sodium hydroxide in dehydrated alcohol. Sodium hydroxide and/or hydrochloric acid 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.

12.2 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

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.

Distribution

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

Gemcitabine pharmacokinetics are linear and are described by a two 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.

Elimination

Metabolism

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

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one 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.

Specific Populations

Geriatric Patients

Clearance of gemcitabine was affected by age. The lower clearance in 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 15 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 15: Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance in males (L/hr/m^2)	Clearance in females (L/hr/m^2)	Half-Life[a] in males (min)	Half-Life[a] in females (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 <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.

Male and Female Patients
Clearance of gemcitabine was affected by gender. Female patients have lower clearance and longer half lives than male patients. Please see Table 15.

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

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

Drug Interaction Studies
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. 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 was mutagenic in an *in vitro* mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine intra-peritonial 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

The safety and efficacy of gemcitabine was studied in a randomized trial (Study 1) 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 1000 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 major efficacy outcome measure was progression free survival (PFS).

A total of 356 patients were randomized, 178 patients to the gemcitabine plus carboplatin arm and 178 patients to the carboplatin arm. Baseline demographics and disease characteristics in gemcitabine plus carboplatin arm were: median age of 59 (range: 36 to 78), 94% ECOG PS 0-1. 8% had evaluable disease and 92% had bidimensionally measurable disease. 40% had 6 to 12 months of platinum free interval, 59% had greater than 12 months platinum free interval; and as first-line therapy, 70% had platinum-taxane combination, 29% had platinum-non-taxane combination and 1% had platinum monotherapy.

Baseline demographics and disease characteristics in carboplatin arm were: median age of 58 (range: 21 to 81), 95% ECOG PS 0-1. 3% had evaluable disease and 96% had bidimensionally measurable disease. 40% had 6 to 12 months of platinum free interval, 60% had greater than 12 months platinum free interval; and as first-line therapy, 71% had platinum-taxane combination, 28% had platinum-non-taxane combination and 1% had platinum monotherapy.

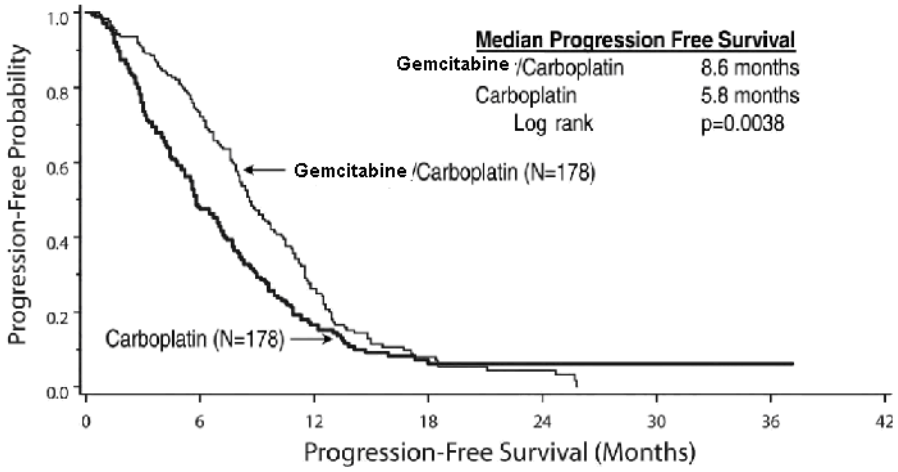
The addition of gemcitabine to carboplatin resulted in statistically significant improvements in PFS and overall response rate as shown in Table 16 and Figure 1. Approximately 75% of patients in each arm received additional chemotherapy for disease progression; 13 of 120 patients in the carboplatin alone arm received gemcitabine for treatment of disease progression. There was no significant difference in overall survival between the treatment arms.

Table 16: Efficacy Results in Study 1

	Gemcitabine /Carboplatin (N=178)	**Carboplatin (N=178)**
Progression-free Survival Median (95% CI[a]) months	8.6 (8.0, 9.7)	5.8 (5.2, 7.1)
Hazard Ratio (95% CI)	0.72 (0.57, 0.90)	
p-value[b]	p=0.0038	
Overall Survival Median (95% CI) months	18.0 (16.2, 20.3)	17.3 (15.2, 19.3)
Hazard Ratio (95% CI)	0.98 (0.78, 1.24)	
p-value[b]	p=0.8977	
Overall Response Rate by investigator	47.2%	30.9%
p-value[c]	p=0.0016	
CR[d] PR plus PRNM[e]	14.6% 32.6%	6.2% 24.7%
Overall Response Rate[f] by independent review	46.3%	35.6%
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 Study 1



14.2 Metastatic Breast Cancer

The safety and efficacy of gemcitabine were evaluated in a randomized, open-label trial (Study 2) 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 1250 mg/m^2 on Days 1 and 8 of a 21-day cycle and paclitaxel 175 mg/m^2 administered prior to gemcitabine 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 major efficacy outcome measure was time to documented disease progression.

A total of 529 patients were randomized in breast cancer, 267 patients to the gemcitabine plus paclitaxel arm and 262 patients to the paclitaxel arm. Baseline demographics and disease characteristics in gemcitabine plus paclitaxel arm were: median age of 53 (range: 26 to 83). 97% had metastatic disease. 70% had baseline KPS $\geq$ 90%; 57% had tumor sites 1 to 2 and 43% had tumor sites greater than or equal to 3; 73% had visceral disease and 97% had prior anthracycline.

Baseline demographics and disease characteristics in paclitaxel arm were: median age of 52 (range: 26 to 75). 97% had metastatic disease. 74% had baseline KPS $\geq$ 90%; 59% had tumor sites 1 to 2 and 41% had tumor sites greater than or equal to 3; 73% had visceral disease and 96% had prior anthracycline.

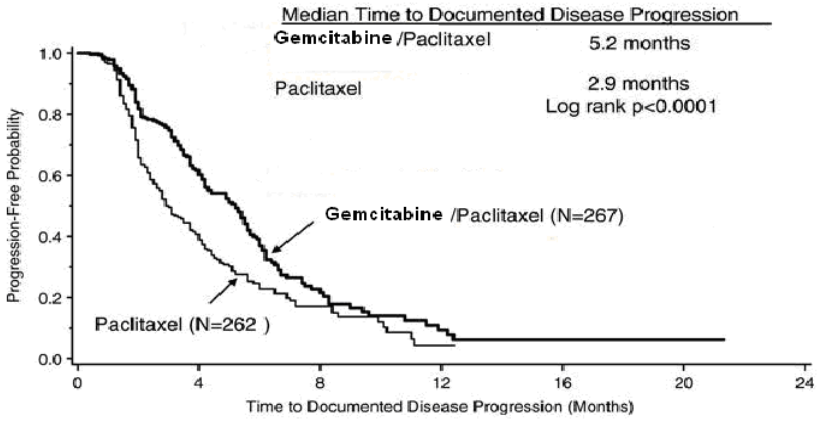
Efficacy results are presented in Table 17 and Figure 2. The addition of gemcitabine to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to paclitaxel alone. There was no significant difference in overall survival.

Table 17: Efficacy Results in Study 2

	Gemcitabine/Paclitaxel, N=267	Paclitaxel, N=262
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	

[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 Disease Progression in Study 2



14.3 Non-Small Cell Lung Cancer (NSCLC)

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

Study 3: 28-Day Schedule

A randomized trial (Study 3) 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 1000 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 major efficacy outcome measure was overall survival. A total of 522 patients were enrolled, 260 patients in gemcitabine plus cisplatin arm and 262 in cisplatin arm. Patient demographics and baseline characteristics in gemcitabine plus cisplatin arm were: 70% males , median age 62 years (range 36 to 88); 7% in stage IIIA, 26% in stage IIIB and 67% stage IV, 41 %; Baseline KPS 70 to 80, 57% Baseline KPS 90 to 100. Patient demographics and baseline characteristics in cisplatin arm were: 71% males, median

age 63 years (range 35 to 79), 7% in stage IIIA, 23% in stage IIIB and 70% stage IV NSCLC, 44 % Baseline KPS 70 to 80, 55% Baseline KPS 90 to 100. Patient demographics and baseline characteristics 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 18 and Figure 3 for overall survival.

Study 4: 21-Day Schedule

A randomized (1:1), multicenter trial (Study 4) was conducted in 135 patients with Stage IIIB or IV NSCLC. Patients were randomized to receive 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 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. A total of 135 patients were enrolled, 69 patients in gemcitabine plus cisplatin arm and 66 in cisplatin arm. Patient demographics and baseline characteristics in gemcitabine plus cisplatin arm were: 93% males , median age 58 years (range 33 to 76); 48% in stage IIIB and 52% stage IV, 45 %; Baseline KPS 70 to 80, 55% Baseline KPS 90 to 100. Patient demographics and baseline characteristics in cisplatin arm were: 92% males, median age 60 years (range 35 to 75), 52% in stage IIIB and 49% stage IV NSCLC, 52% Baseline KPS 70 to 80, 49% Baseline KPS 90 to 100.

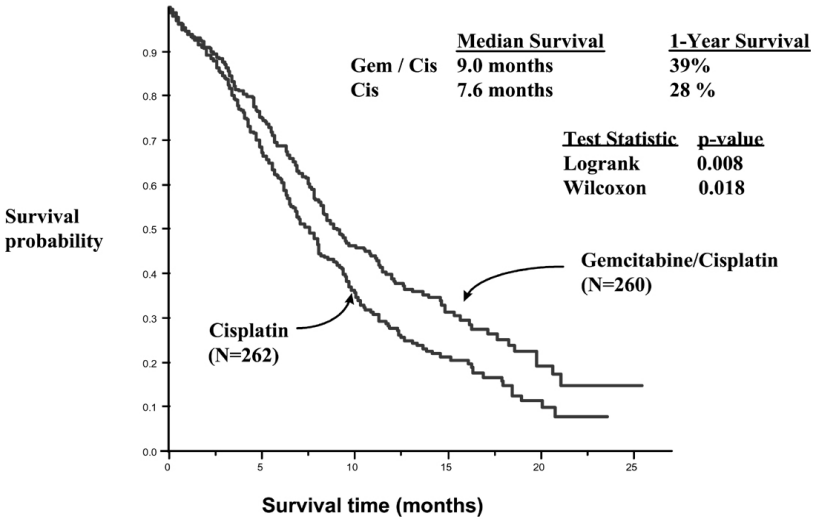
Efficacy results for Studies 3 and 4 are summarized in Table 18. There was no significant difference in survival between the two treatment arms (see Table 18).

Table 18: Efficacy Results for Studies 3 and 4

Trial	**28-day Schedule[a] (Study 3)**		**21-day Schedule[b](Study 4)**	
Treatment Arm	Gemcitabine plus Cisplatin	Cisplatin	Gemcitabine plus Cisplatin	Etoposide plus Cisplatin
Efficacy Outcomes				
Survival				
Median in months	9.0	7.6	8.7	7.0
(95% CI[e]) months	8.2, 11.0	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	3.0, 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 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] 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.

Figure 3: Kaplan-Meier Survival Curves in Study 3



14.4 Pancreatic Cancer

The safety and efficacy of gemcitabine was evaluated in two trials (Studies 5 and 6), a randomized, single-blind, two-arm, active-controlled trial (Study 5) 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 (Study 6) conducted in patients with locally advanced or metastatic pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. Study 5 randomized patients to receive gemcitabine 1000 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 Study 6, all patients received gemcitabine 1000 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 major 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:

- 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
- 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.

Study 5 enrolled 126 patients in the US and Canada. The demographic and entry characteristics were similar between gemcitabine arm and cisplatin arm. The efficacy outcome results are

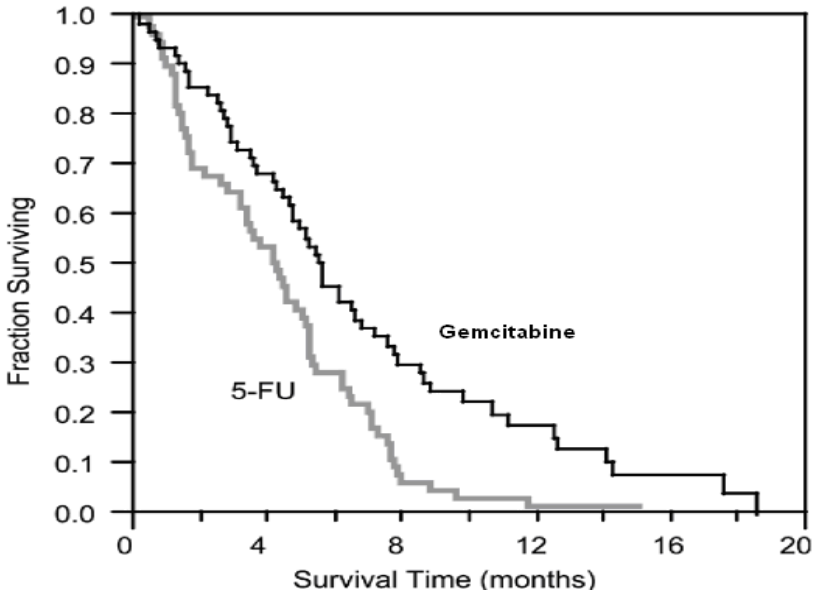
shown in Table 19 and Figure 4. Patient demographics and baseline characteristics in gemcitabine arm were: 54% males, 62 years median age (range 37 to 79); 71% stage IV disease; 70% Baseline KPS ≤70. Patient demographics and baseline characteristics in 5-FU were: 54% males, 61 years median age (range 36 to 77); 71% stage IV disease; 68% Baseline KPS ≤70.

Table 19: Efficacy Results in Study 5

	Gemcitabine N= 63	**5-FU N= 63**
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.



15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemcitabine Injection is a clear colorless to pale yellow solution available in sterile multiple-dose vials containing:

Vial	NDC number
200 mg/2 mL (100 mg/mL)	16729-391-30
1 g/10 mL (100 mg/mL)	16729-419-03
1.5 g/15 mL (100 mg/mL)	16729-423-33
2 g/ 20 mL (100 mg/mL)	16729-426-05

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15° C and 30°C (59°F and 86°F).

After initial puncture, Gemcitabine Injection multiple-dose vials are stable for 28 days when stored at room temperature.

Gemcitabine is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Myelosuppression

Advise patients of the risk of myelosuppression and instruct them to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur *[see Warnings and Precautions (5.2)]*.

Pulmonary toxicity

Advise patients of the risks of pulmonary toxicity including respiratory failure and death and instructed to immediately contact their healthcare provider for development of shortness of breath, wheezing, or cough *[see Warnings and Precautions (5.3)]*.

Hemolytic-uremic syndrome and renal failure

Advise patients of the risks of hemolytic-uremic syndrome and associated renal failure and instructed 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)]*.

Hepatotoxicity

Advise patients of the risks of hepatic toxicity including liver failure and death and instructed 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)]*.

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that Gemcitabine Injection can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use

effective contraception during treatment with and for 6 months after the final dose of Gemcitabine Injection. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with and for 3 months after the final dose of Gemcitabine Injection *[see Warnings and Precaution (5.6) and Use in Specific Populations (8.1) and (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with and for one week after the final dose of Gemcitabine Injection *[see Use in Specific Populations (8.2)]*.

Fertility Effects

Advise males of reproductive potential of the potential for reduced fertility with Gemcitabine Injection use *[see Use in Specific Populations (8.3)]*.

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