HIGHLIGHTS OF PRESCRIBING INFORMATION

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

GEMCITABINE for injection, powder, lyophilized, for solution, for intravenous use

Initial U.S. Approval: 1996

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

Warnings and Precautions,
Hemolytic Uremic Syndrome (5.4)
5/2019

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

Gemcitabine for 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 for Injection is for intravenous use only.

- Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.1)
- Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. (2.2)
- Non-Small Cell Lung Cancer: 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 for Injection: 200 mg or 1 gram lyophilized powder in single-dose vials for reconstitution. (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 for Injection for unexplained dyspnea or other evidence of severe pulmonary toxicity. (5.3)
- Hemolytic Uremic Syndrome (HUS): Monitor renal function prior to initiation and during treatment. Discontinue Gemcitabine for Injection for HUS or severe renal impairment. (5.4)
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during treatment. Discontinue Gemcitabine for Injection for severe hepatic toxicity. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential to use effective contraception. (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 for Injection. (5.8)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue Gemcitabine for Injection. (5.9)

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

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

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

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2020

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 in combination with cisplatin is indicated for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC).

1.4 Pancreatic Cancer

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

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dosage of Gemcitabine for Injection, USP is 1000 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with carboplatin AUC 4 administered intravenously on Day 1 after Gemcitabine for Injection, USP administration. Refer to carboplatin prescribing information for additional information.

Dosage Modifications

Recommended Gemcitabine for Injection, USP dosage modifications for myelosuppression are described in Tables 1 and 2 *[see Warnings and Precautions (5.2)]*. Refer to the recommended dosage modifications for non-hematologic adverse reactions *[see Dosage and Administration (2.5)]*.

Table 1: Recommended Dosage Modifications for Gemcitabine for Injection, USP for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment Day	Absolute Neutrophil Count (x 10^6/L)	Platelet Count (x 10

Occurrence	Myelosuppression During Treatment Cycle	Dosage Modification
Initial Occurrence	• Absolute neutrophil count less than 500 x 10^6/L for more than 5 days or • Absolute neutrophil count less than 100 x 10^6/L for more than 3 days or • Febrile neutropenia or • Platelets less than 25,000x10^6/L or • Cycle delay for more than one week due to toxicity	Permanently reduce Gemcitabine for Injection, USP 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, USP to 800 mg/m^2 on Day 1 only

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dosage of Gemcitabine for Injection, USP is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with paclitaxel 175 mg/m^2 administered as a 3-hour intravenous infusion on Day 1 before Gemcitabine for Injection, USP administration. Refer -

- Exercise caution and wear gloves when preparing Gemcitabine for Injection, USP solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemcitabine for Injection, USP contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.
- Reconstitute the 200 mg vial with 5 mL and the 1 gram vial with 25 mL of 0.9% Sodium Chloride Injection, USP to yield a Gemcitabine for Injection, USP concentration of 38 mg per mL. Reconstituted Gemcitabine for Injection, USP is a clear, colorless to light straw-colored solution.
- Visually inspect reconstituted product for particulate matter and discoloration. Discard if particulate matter or discoloration is observed.
- Withdraw the calculated dose from the vial and discard any unused portion.
- Prior to administration, dilute the reconstituted solution with 0.9% Sodium Chloride Injection, USP to a minimum final concentration of at least 0.1 mg per mL.
- Store Gemcitabine for Injection, USP solutions (reconstituted and diluted) at controlled room temperature of 20 ° to 25 ℃ (68 ° to 77 ℉). Do not refrigerate as crystallization can occur. Discard Gemcitabine for Injection, USP solutions if not used within 24 hours after reconstitution.
- No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS

Gemcitabine for Injection, USP: 200 mg gemcitabine or 1 gram gemcitabine as a sterile white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Schedule-Dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of Gemcitabine for Injection, 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 for Injection is influenced by the length of the infusion *[see Clinical Pharmacology (12.3)]*. Refer to the recommended Gemcitabine for Injection dosage *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)]*.

5.2 Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with Gemcitabine for Injection as a single agent and the risks are increased when Gemcitabine for Injection is combined with other cytotoxic drugs. In clinical trials, Grade 3 or 4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of the 979 patients who received single agent Gemcitabine for Injection. The frequencies of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8% to 28%, and 5% to 55%, respectively, in patients receiving Gemcitabine for Injection in combination with another drug *[see Adverse Reactions (6.1)]*.

Prior to each dose of Gemcitabine for Injection, obtain a complete blood count (CBC) with a differential and a platelet count. Modify the dosage as recommended *[see Dosage and Administration (2.1, 2.2, 2.3, 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 the discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks afte

during treatment with Gemcitabine for Injection and for 3 months following the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.7 Exacerbation of Radiation Therapy Toxicity

Gemcitabine for Injection is not recommended 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 for Injection 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 >7 days apart)

Excessive toxicity has not been observed when Gemcitabine for Injection is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who received 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 for Injection as a single agent or in combination with other chemotherapeutic agents *[see Adverse Reactions (6.2)]*. Permanently discontinue Gemcitabine for Injection if CLS develops during therapy.

5.9 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving Gemcitabine for Injection as a single agent or in combination with other chemotherapeutic agents *[see Adverse Reactions (6.2)]*. PRES can present with headache, seizure, lethargy, ET0adacheurre/F1 12 Tf(c).4<0058

Single Agent

The data described below reflect exposure to Gemcitabine for Injection as a single agent administered at doses between 800 mg/m^2 to 1250 mg/m^2 intravenously over 30 minutes once weekly in 979 patients with various malignancies. The most common (≥20%) adverse reactions of single agent Gemcitabine for Injection are nausea/vomiting, anemia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (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, increased 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 reactions (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension) and adverse reactions resulting in discontinuation of Gemcitabine for Injection in <1% of 979 patients were anemia, thrombocytopenia, hepatic dysfunction, renal dysfunction, nausea/vomiting, fever, rash, dyspnea, hemorrhage, infection, stomatitis, somnolence, flu-like syndrome, and edema.

Tables 5 and 6 present the incidence of selected adverse reactions and laboratory abnormalities reported in patients with various malignancies receiving single agent Gemcitabine for Injection across 5 clinical trials. Additional clinically significant adverse reactions are provided following Table 6.

Table 5: Selected Adverse Reactions Occurring in Patients Receiving Single Agent Gemcitabine for Injection[a]

Adverse Reactions[b]	**Gemcitabine for Injection**

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 WHO.
[b] Regardless of causality.
[c] N=699 to 974; all patients with laboratory or non-laboratory data.

Additional adverse reactions include the following:

- Transfusion requirements: Red blood cell transfusions (19%); platelet transfusions (<1%)
- Edema: Edema (13%), peripheral edema (20%), 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

Ovarian Cancer

Tables 7 and 8 present the incidence of selected adverse reactions and laboratory abnormalities, occurring in ≥10% of gemcitabine for injection-treated patients and at a higher incidence in the Gemcitabine for Injection with carboplatin arm, reported in a randomized trial (Study 1) of Gemcitabine for Injection with 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 <10% of patients, are provided following Table 8.

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 adverse reactions (11% versus 10%), were similar between arms. Dose adjustment for Gemcitabine for Injection occurred in 10% of patients and Gemcitabine for Injection dose was omitted in 14% of patients in the Gemcitabine for Injection/carboplatin arm.

Table 7: Adverse Reactions Occurring in >10% of Patients Receiving Gemcitabine with Carboplatin and at Higher -4)] in Study 1[a]

Adverse Reactions[b]	**Gemcitabine for Injection/Carboplatin (N=175)**			**Carboplatin (N=174)**		
	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 CTC Version 2.0.
[b] Regardless of causality.

Table 8: Laboratory Abnormalities Occurring in Patients Receiving Gemcitabine with Carboplatin and at Higher Incidence than

-4)] in Study 1[a]

Laboratory Abnormality[b]	**Gemcitabine for Injection/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 CTC Version 2.0.

Adverse Reactions[b]	Gemcitabine for Injection/Paclitaxel (N=262)			Paclitaxel (N=259)
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	

higher for patients receiving Gemcitabine for Injection with cisplatin compared to those receiving cisplatin alone. The incidence of febrile neutropenia (3% versus <1%), sepsis (4% versus 1%), Grade 3 cardiac dysrhythmias (3% versus <1%) were all higher in the Gemcitabine for Injection with 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 11: Selected Adverse Reactions Higher Incidence than in Patients Receiving Single Agent Cisplatin -4)] in Study 3[a]

Adverse Reactions[b]	Gemcitabine for Injection/Cisplatin[c]			Cisplatin[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

Renal						
Increased 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] Grade based on National Cancer Institute CTC.
[b] Regardless of causality.
[c] N=217 to 253; all Gemcitabine for Injection/cisplatin patients with laboratory or non-laboratory data.
[d] N=213 to 248; all cisplatin patients with laboratory or non-laboratory data.
[e] Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events.

Tables 13 and 14 present the incidence of selected adverse reactions and laboratory abnormalities occurring in ≥10% of Gemcitabine for Injection-treated patients and at a higher incidence in the Gemcitabine for Injection with cisplatin arm, reported in a randomized trial (Study 4) of Gemcitabine for Injection with cisplatin (n=69) administered in 21-day cycles as compared to etoposide with cisplatin (n=66) in patients receiving first-line treatment for locally advanced or metastatic NSCLC *[see Clinical Studies (14.3)]*. Additional clinically significant adverse reactions are provided following Table 14.

Patients in the Gemcitabine for Injection/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 adverse reactions was 22% in the GC arm and 27% in the EC arm. The proportion of patients who discontinued treatment for adverse reactions was higher in the GC arm (14% versus 8%). The proportion of patients who were 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 GC arm.

Table 13: Selected Adverse Reactions in Patients Receiving Gemcitabine with Cisplatin in Study 4[a]

Adverse Reactions[b]	**Gemcitabine for Injection/Cisplatin[c]**			**Etoposide/Cisplatin[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[e]	12	-	-	2	-	-
Rash	10	0	0	3	0	0
Hemorrhage	9	0	3	3	0	3
Fever	6	0	0	3	0	0
Somnolence	3	0	0	3	2	0
Flu-like Syndrome[e]	3	-	-	0	-	-
Dyspnea	1	0	1	3	0	0

[a] Grade based on criteria from the WHO.
[b] Non-laboratory events were graded only if assessed to be possibly drug-related. Pain data were not collected.
[c] N=67 to 69; all Gemcitabine for Injection/cisplatin patients with laboratory or non-laboratory data.
[d] N=57 to 63; all Etoposide/cisplatin patients with laboratory or non-laboratory data.

[e] Flu-like syndrome and edema were not graded.

Table 14: Selected Laboratory Abnormalities Occurring in Patients Receiving Gemcitabine with Cisplatin in Study 4[a]

Laboratory Abnormality[b]	Gemcitabine for Injection/Cisplatin[c]	Etoposide/Cisplatin

Based on animal data and its mechanism of action, Gemcitabine for Injection can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of Gemcitabine for Injection in pregnant women. In animal reproduction studies, gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits *(see Data)*. Advise pregnant women of the potential risk to a fetus *[see Use in Special Populations (8.3)]*.

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

Data

Animal Data

Gemcitabine is embryotoxic in mice. Daily dosing of gemcitabine to pregnant mice increased the incidence of fetal malformation (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day [approximately 0.005 times the 1000 mg/m^2 clinical dose based on body surface area (BSA)]. Gemcitabine was embryotoxic and fetotoxic in rabbits. Daily dosing of gemcitabine to pregnant rabbits resulted in fetotoxicity (decreased fetal viability, reduced litter sizes, and developmental delays) and increased the incidence of fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day (approximately 0.002 times the 1000 mg/m^2 clinical dose based on BSA).

8.2 Lactation

Risk Summary

There is no information regarding the presence of Gemcitabine for Injection or its metabolites in human milk, or their effects on the breastfed infant or on milk production. Due to the potential for serious adverse reactions in breastfed infants from Gemcitabine for Injection, advise women not to breastfeed during treatment with Gemcitabine for Injection and for at least one week following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating Gemcitabine for Injection *[see Use in Specific Populations (8.1)]*.

Contraception

Gemcitabine for Injection can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Because of the potential for genotoxicity, advise females of reproductive potential to use effective contraception during treatment with Gemcitabine for Injection and for 6 months after the final dose of Gemcitabine for Injection.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with Gemcitabine for Injection and for 3 months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on animal studies, Gemcitabine for Injection may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*. It is not known whether these effects on fertility are reversible.

8.4 Pediatric Use

The safety and effectiveness of Gemcitabine for 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 for Injection 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, increased serum transaminases, nausea, and rash/desquamation. No meaningful clinical activity was observed in this trial.

8.5 Geriatric Use

In clinical studies which enrolled 979 patients with various malignancies who received single agent Gemcitabine for Injection, 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 or 4 thrombocytopenia in older patients as compared to younger patients.

In a randomized trial in women with ovarian cancer (Study 1), 175 women received Gemcitabine for Injection with 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 *[see Dosage and Administration (2.1)]*.

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

8.6 Gender

Gemcitabine for Injection clearance is decreased in females *[see Clinical Pharmacology (12.3)]*. In single agent studies of Gemcitabine for Injection, 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, 2.2, 2.3, 2.4)]*.

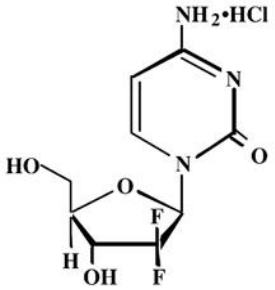
10 OVERDOSAGE

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, monitor with appropriate blood counts and provide supportive therapy, as necessary.

11 DESCRIPTION

Gemcitabine is a nucleoside metabolic inhibitor. Gemcitabine hydrochloride, USP is 2 ′-deoxy-2 ′,2 ′-difluorocytidine monohydrochloride (β-isomer) with the following structural formula:



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

Gemcitabine hydrochloride, USP is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine for Injection, USP (gemcitabine) is a sterile white to off-white lyophilized powder and available as 200 mg and 1 gram single-dose vials for intravenous use only. Each 200 mg vial contains 200 mg gemcitabine (equivalent to 227.7 mg gemcitabine hydrochloride), 200 mg mannitol and 12.5 mg sodium acetate. Each 1 gram vial contains 1 gram gemcitabine (equivalent to 1.139 gram gemcitabine hydrochloride), 1 gram mannitol, and 62.5 mg sodium acetate. 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

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 mg/m^2 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 <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 sex. 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 of radiolabeled drug as a 30-minute infusion. 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 geriatric patients 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 sex.

Table 15: Gemcitabine Clearance and Half-

Age	Clearance Men	Clearance Women	Half-Life[a] Men	Half-Life[a] Women

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 for Injection (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in patients with NSCLC, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. Data from patients with NSCLC demonstrate that Gemcitabine for Injection 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.

Data from metastatic breast cancer patients shows that 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.

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 intraperitoneal doses of 0.5 mg/kg/day [about 1/700 the 1000 mg/m^2 clinical dose based on body surface area (BSA)] in male mice resulted in 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 1000 mg/m^2 clinical dose based on BSA) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the 1000 mg/m^2 clinical dose based on BSA).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

The efficacy of Gemcitabine for Injection was evaluated in a randomized trial (Study 1) conducted in 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 for Injection 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle with carboplatin AUC 4 on Day 1 after Gemcitabine for Injection administration (n=178) or carboplatin AUC 5 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 enrolled. Demographics and baseline characteristics are shown in Table 16.

Efficacy results are presented in Table 17 and Figure 1. The addition of Gemcitabine for Injection to carboplatin resulted in statistically significant improvements in PFS and overall response rate. 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 Injection for treatment of disease progression. There was no significant difference in overall survival between the treatment arms.

Table 16: Baseline Demographics and Clinical Characteristics for Study 1

	Gemcitabine for Injection/Carboplatin (N=178)	**Carboplatin (N=178)**
Median age, years	59	58
Range	36 to 78	21 to 81
Baseline ECOG performance status 0 to 1[a]	94%	95%
Disease Status		
Evaluable	8%	3%
Bidimensionally measurable	92%	96%
Platinum-free interval[b]		
6 to 12 months	40%	40%
>12 months	59%	60%
First-line therapy		
Platinum-taxane combination	70%	71%
Platinum-non-taxane combination	29%	28%
Platinum monotherapy	1%	1%

[a] 5 patients on Gemcitabine for Injection with carboplatin arm and 4 patients on carboplatin arm had no baseline Eastern Cooperative Oncology Group (ECOG) performance status.

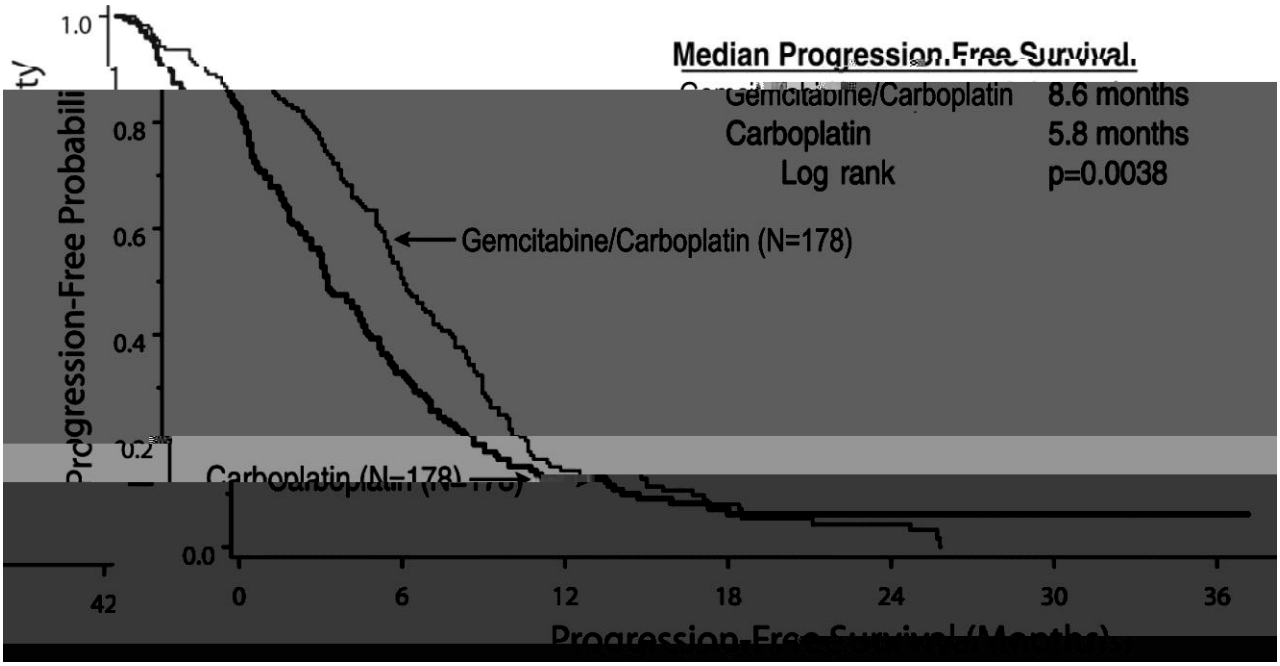
[b] 2 patients on Gemcitabine for Injection with carboplatin arm and 1 patient on carboplatin arm had platinum-free interval <6 months.

Table 17: Efficacy Results in Study 1

Efficacy Parameter	**Gemcitabine for Injection/Carboplatin (N=178)**	**Carboplatin (N=178)**
Progression-Free Survival		
Median (95% CI[a]) in 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) in 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 Review	47.2%	30.9%
p-value[c]	p=0.0016	
CR[d]	14.6%	6.2%
PR with PRNM[e]	32.6%	24.7%
Overall Response Rate[f] by Independent Review	46.3%	35.6%
p-value[c]	p=0.11	
CR[d]	9.1%	4.0%
PR with PRNM[e]	37.2%	31.7%

[a] CI=confidence interval.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in Study 1



14.2 Breast Cancer

The efficacy of Gemcitabine for Injection was evaluated in a multinational, randomized, open-label trial (Study 2) conducted in women receiving initial treatment for metastatic breast cancer and who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Patients were randomized to receive either Gemcitabine for Injection 1250 mg/m^2 on Days 1 and 8 of each 21-day cycle with paclitaxel 175 mg/m^2 administered on Day 1 before Gemcitabine for Injection administration (n=267) or paclitaxel 175 mg/m^2 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 enrolled. Demographic and baseline characteristics were similar between treatment arms (Table 18).

Efficacy results are presented in Table 19 and Figure 2. The addition of Gemcitabine for Injection 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 18: Baseline Demographics and Clinical Characteristics for Study 2

	Gemcitabine for Injection/Paclitaxel (N=267)	**Paclitaxel (N=262)**
Median age (years)	53	52

≥3	43%	41%
Visceral disease	73%	73%
Prior anthracycline	97%	96%

[a] Karnofsky Performance Status.

Table 19: Efficacy Results in Study 2

Efficacy Parameter	**Gemcitabine for Injection/Paclitaxel (N=267)**	**Paclitaxel (N=262)**
Time to Documented Disease Progression[a]		
Median (95% CI) in months	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[b]		
Median (95% CI) in months	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	40.8%	22.1%
(95% CI)	(34.9, 46.7)	(17.1, 27.2)
p-value	p<0.0001	

[a] These represent reconciliation of investigator and Independent Review Committee assessments according to a predefined algorithm.

[b] Based on the ITT population.

Figure 2: Kaplan-Meier Curves for Time to Documented Disease Progression in Study 2

14.3 Non-Small Cell Lung Cancer

The efficacy of Gemcitabine for Injection was evaluated in two randomized, multicenter trials.

Study 3: 28-Day Schedule

A multinational, randomized trial (Study 3) compared Gemcitabine for Injection with 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 either Gemcitabine for Injection 1000 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle with cisplatin 100 mg/m^2 on Day 1 after Gemcitabine for Injection administration (N=260) or cisplatin 100 mg/m^2 on Day 1 of each 28-day cycle (N=262). The major efficacy outcome measure was overall survival.

A total of 522 patients were enrolled. Demographics and baseline characteristics (Table 20) 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 for Injection with cisplatin arm having adenocarcinoma.

Efficacy results are presented in Table 21 and Figure 3.

Study 4: 21-Day Schedule

A randomized (1:1), multicenter trial (Study 4) was conducted in patients with Stage IIIB or IV NSCLC. Patients were randomized to receive either Gemcitabine for Injection 1250 mg/m^2 on Days 1 and 8 of each 21-day cycle with cisplatin 100 mg/m^2 on Day 1 after Gemcitabine for Injection administration or etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 with cisplatin 100 mg/m^2 on Day 1 of each 21-day cycle. The major efficacy outcome measure was response rate.

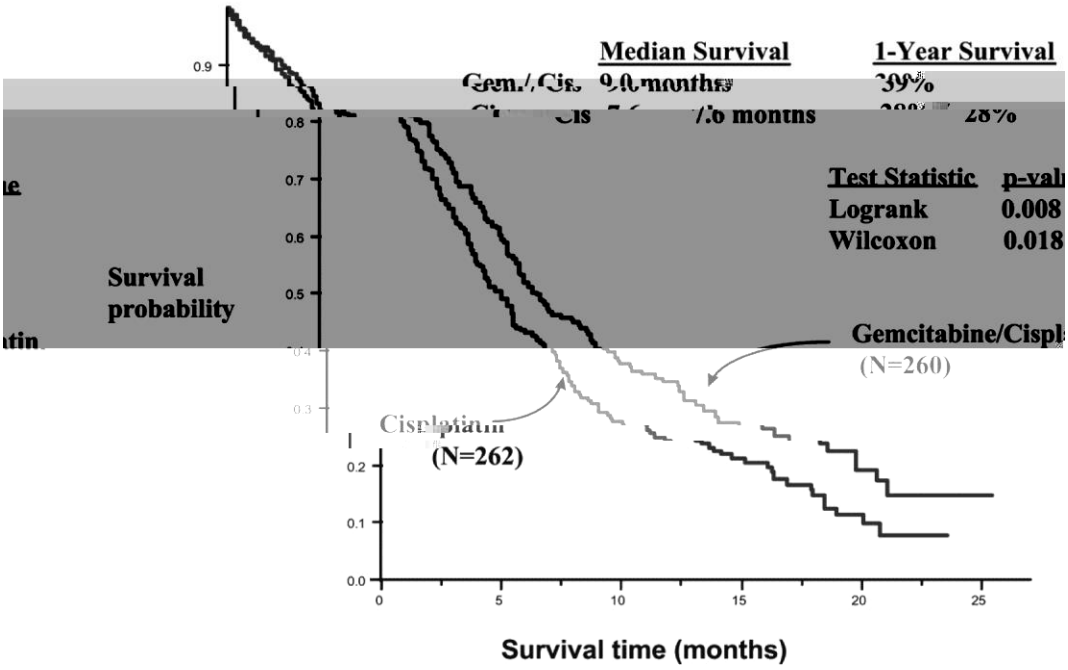
A total of 135 patients were enrolled. Demographics and baseline characteristics are summarized in Table 20.

Efficacy results are presented in Table 21. There was no significant difference in survival between the two treatment arms. The median survival was 8.7 months for the Gemcitabine for Injection with cisplatin arm versus 7 months for the etoposide with cisplatin arm. Median time to disease progression for the Gemcitabine 1 378.17 T0 0 1 558.1 364.37 Tm0 g0 G[( )593(0abine 1 378.17 T0 0 1 558.1 364.37 Tm0 g0

Efficacy Parameter	Gemcitabine for Injection/Cisplatin (N=260)	Cisplatin (N=262)	Gemcitabine for Injection/Cisplatin (N=69)	Etoposide/Cisplatin (N=66)
Survival				
Median (95% CI[a]) in months	9.0 (8.2, 11.0)	7.6 (6.6, 8.8)	8.7 (7.8, 10.1)	7.0 (6.0, 9.7)
p-value[f]	p=0.008		p=0.18	
Time to Disease Progression				
Median (95% CI[a]) in months	5.2 (4.2, 5.7)	3.7 (3.0, 4.3)	5.0 (4.2, 6.4)	4.1 (2.4, 4.5)
p-value[b]	p=0.009		p=0.015	
Tumor Response	26%	10%	33%	14%
p-value[b]	p<0.0001		p=0.01	

[a] CI=confidence intervals.
[b] p-value two-sided Fisher's Exact test for difference in binomial proportions; log rank test for time-to-event analyses.

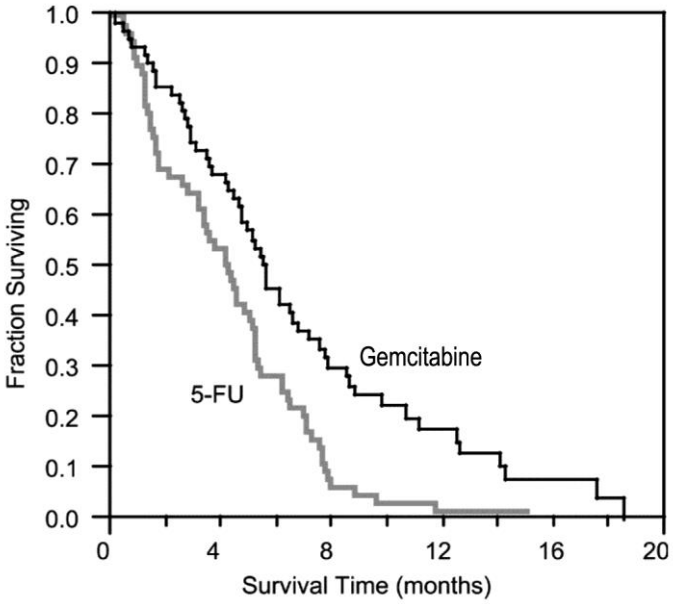
Figure 3: Kaplan-Meier Curves for Overall Survival in Study 3



14.4 Pancreatic Cancer

The efficacy of Gemcitabine for Injection 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 fluorouracil or a fluorouracil-containing regimen. In Study 5, patients were randomized to receive either Gemcitabine for Injection 1000 mg/m^2 intravenously over 30 minutes once weekly for 7 weeks followed by a one-week rest, then once weekly for 3 consecutive weeks every 28-days in subsequent cycles (n=63) or fluorouracil 600 mg/m^2 intravenously over 30 minutes once weekly (n=63). In Study 6, all patients received Gemcitabine for Injection 1000 mg/m^2 intravenously

Figure 4: Kaplan-Meier Curves for Overall Survival in Study 5



15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Gemcitabine for Injection, USP is supplied as follows:

NDC	Gemcitabine for Injection, USP	Package Factor
25021-234-10	200 mg Single-Dose Vial	1 vial per carton
25021-235-50	1 gram Single-Dose Vial	1 vial per carton

Gemcitabine for Injection, USP is a white to off-white, lyophilized powder.

Discard unused portion.

Sterile, Nonpyrogenic, Preservative-free.
The container closure is not made with natural rubber latex.

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

Store at controlled room temperature 20 ° to 25 ℃ (68 ° to 77 ℉); excursions permitted between 15 ° and 30 ℃ (59 ° and 86 ℉). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Myelosuppression

Advise patients of the risks of myelosuppression. Instruct patients to immediately contact their healthcare provider should any signs or symptoms of infection, including fever, or if bleeding or signs of anemia, occur *[see Warnings and Precautions (5.2)]*.

Pulmonary Toxicity
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)]*.

Hemolytic Uremic Syndrome and Renal Failure
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)]*.

Hepatic Toxicity
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)]*.

Embryo-Fetal Toxicity
Advise females and males of reproductive potential that Gemcitabine for Injection can cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment with Gemcitabine for Injection and for 6 months after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Gemcitabine for Injection and for 3 months after the final dose *[see Warnings and Precaution (5.6), Use in Specific Populations (8.1, 8.3)]*.

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

Infertility
Advise males of reproductive potential of the potential for reduced fertility with Gemcitabine for Injection *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

SAGENT®

Mfd. for SAGENT Pharmaceuticals
Schaumburg, IL 60195 (USA)
Made in China

Revised: March 2020