GEMCITABINE- gemcitabine injection, solution
Ingenus Pharmaceuticals, LLC

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

RECENT MAJOR CHANGES

Warnings and Precautions, Hemolytic Uremic Syndrome (5.4) 6/2019

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 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

Injection: 200 mg/5.26 mL (38 mg/mL), 1 g/26.3 mL (38 mg/mL), or
2 g/52.6 mL (38 mg/mL) in a single-dose vial. (3)

CONTRAINDICATIONS

Patients with a known hypersensitivity to gemcitabine. (4)

WARNINGS AND PRECAUTIONS

- Schedule-Dependent Toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly. (5.1)
- Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression. (5.2)
- Pulmonary Toxicity and Respiratory Failure: Discontinue Gemcitabine 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 Injection for HUS or severe renal impairment. (5.4)
- Hepatic Toxicity: Monitor hepatic function prior to initiation and during treatment. 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 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 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, 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 Ingenus Pharmaceuticals, LLC at 1-877-748-1970 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: 9/2019

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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 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 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 fluorouracil.

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dosage of Gemcitabine Injection 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 Injection administration. Refer to carboplatin prescribing information for additional information.

Dosage Modifications

Recommended dosage modifications for Gemcitabine Injection 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 Injection for Myelosuppression on Day of Treatment in Ovarian Cancer

Treatment	Absolute Neutrophil		Platelet Count	Dosage Modification

day	Count (x 10^6 /L)		(x 10^6 /L)	
Day 1	Greater than or equal to 1500	And	Greater than or equal to 100,000	None
	Less than 1500	Or	Less than 100,000	Delay Treatment Cycle
Day 8	Greater than or equal to 1500	And	Greater than or equal to 100,000	None
	1000 to 1499	Or	75,000 to 99,999	50% of full dose
	Less than 1000	Or	Less than 75,000	Hold

Table 2: Recommended Dosage Modifications for Gemcitabine Injection for Myelosuppression in Previous Cycle in Ovarian Cancer

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 25,000 x $10^{6/}$/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 dosage of Gemcitabine Injection is 1250 mg/m^2intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with paclitaxel 175 mg/m^2administered as a 3-hour intravenous infusion on Day 1 before Gemcitabine Injection administration. Refer to paclitaxel prescribing information for additional information.

Dosage Modifications

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

Table 3: Recommended Dosage Modifications for Gemcitabine Injection for Myelosuppression on Day of Treatment in Breast Cancer

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

Day 1	Greater than or equal to 1500	And	Greater than or equal to 100,000	None
	Less than 1500	Or	Less than 100,000	Hold
Day 8	Greater than or equal to 1200	And	Greater than 75,000	None
	1000 to 1199	Or	50,000 to 75,000	75% of full dose
	700 to 999	And	Greater than or equal to 50,000	50% of full dose
	Less than 700	Or	Less than 50,000	Hold

2.3 Non-Small Cell Lung Cancer

Recommended Dose and Schedule

28-day schedule

The recommended dosage of Gemcitabine Injection is 1000 mg/m^2 intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle in combination with cisplatin 100 mg/m^2 administered intravenously on Day 1 after Gemcitabine Injection administration.

21-day schedule

The recommended dosage of Gemcitabine Injection is 1250 mg/m^2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle in combination with cisplatin 100 mg/m^2 administered intravenously on Day 1 after Gemcitabine Injection administration.

Refer to cisplatin prescribing information for additional information.

Dosage Modifications

Recommended dosage modifications for Gemcitabine Injection myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to the recommended dosage modifications for non-hematologic adverse reactions *[see Dosage and Administration (2.5)]*.

2.4 Pancreatic Cancer

Recommended Dose and Schedule

The recommended dosage of Gemcitabine Injection is 1000 mg/m^2 intravenously over 30 minutes. The recommended treatment schedule is as follows:

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

Dosage Modifications

Recommended dosage modifications for Gemcitabine Injection for myelosuppression are described in Table 4 *[see Warnings and Precautions (5.2)]*. Refer to the recommended dosage modifications for non-hematologic adverse reactions *[see Dosage and Administration (2.5)]*.

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

Absolute Neutrophil Count (x 10^6/L)		Platelet count (x 10^6/L)	Dosage Modification
Greater than or equal to 1000	And	Greater than or equal to 100,000	None
500 to 999	Or	50,000 to 99,999	75% of full dose
Less than 500	Or	Less than 50,000	Hold

2.5 Dosage Modifications for Non-Hematologic Adverse Reactions

Permanently discontinue Gemcitabine Injection for any of the following:

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

Withhold Gemcitabine Injection or reduce dose by 50% for other Grade 3 or 4 non-hematological adverse reactions until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

2.6 Preparation

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 for Intravenous Infusion Administration

- Withdraw the calculated dose from the vial and discard any unused portion.
- Prior to administration, dilute the appropriate amount of drug with 0.9% Sodium Chloride Injection to a minimum final concentration of at least 0.1 mg/mL.
- Store diluted Gemcitabine Injection solution for no more than 24 hours at controlled room temperature of 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Discard if not used within 24 hours after dilution.
- Visually inspect for particulate matter or discoloration prior to administration and discard if particulate matter or discoloration is observed.
- No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/5.26 mL (38 mg/mL), 1 g/26.3 mL (38 mg/mL), and 2 g/52.6 mL (38 mg/mL) as a clear and colorless to light straw-colored solution in a single-dose vial.

4 CONTRAINDICATIONS

Gemcitabine Injection 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, 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 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 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 the 979 patients who received 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)]*.

Prior to each dose of Gemcitabine 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 after the last dose of gemcitabine *[see Adverse Reactions (6.1,6.2)]*.

Permanently discontinue Gemcitabine Injection in patients who develop unexplained dyspnea, with or without bronchospasm, or evidence of severe pulmonary toxicity.

5.4 Hemolytic Uremic Syndrome

Hemolytic uremic syndrome (HUS), including fatalities from renal failure or the requirement for dialysis, can occur with gemcitabine. In clinical trials, HUS occurred in 0.25% of 2429 patients. Most fatal cases of renal failure were due to HUS *[see Adverse Reactions (6.1)]*. Serious cases of thrombotic microangiopathy (TMA) other than HUS have been reported with gemcitabine *[see Adverse Reactions (6.2)]*.

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; increased bilirubin or LDH; reticulocytosis; severe thrombocytopenia; or evidence of renal failure (increased serum creatinine or BUN). Permanently discontinue Gemcitabine Injection in patients with HUS or severe renal impairment. Renal failure may not be reversible even with the discontinuation of therapy.

5.5 Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or with other potentially hepatotoxic drugs *[see Adverse Reactions (6.1, 6.2)]*. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of 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 who develop severe hepatic toxicity.

5.6 Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, Gemcitabine Injection can cause fetal harm when administered to a pregnant woman. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits.

Advise pregnant women of the potential risk to a fetus.

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 treatment with Gemcitabine 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 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 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 is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who received 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 *[see Adverse Reactions (6.2)]*. 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 *[see Adverse Reactions (6.2)]*. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI). Permanently discontinue Gemcitabine Injection if PRES develops during therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- 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)]*
- Exacerbation of Radiation Therapy Toxicity *[see Warnings and Precautions (5.7)]*
- Capillary Leak Syndrome *[see Warnings and Precautions (5.8)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

Single Agent

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 intravenously over 30 minutes once weekly, in 979 patients with various malignancies. The most common (≥20%) adverse reactions of single agent gemcitabine 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 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 <1% of 979 patient 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 across 5 clinical trials. Additional clinically significant adverse reactions are provided following Table 6.

Table 5: Selected Adverse Reactions Occurring in ≥ 10% of Patients Receiving Single Agent Gemcitabine[a]

Adverse Reactions[b]	Gemcitabine[c]		
	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] For approximately 60% of patients, non-laboratory adverse events were graded only if assessed to be possibly drug-related.

[c] N=699-974; all patients with laboratory or non-laboratory data.

Table 6: Selected Laboratory Abnormalities Occurring in Patients Receiving Single Agent Gemcitabine[a]

Laboratory Abnormality[b]	Gemcitabine[c]		
	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 WHO.
[b] Regardless of causality.
[c] N=699-974; 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%), and generalized edema (<1%)
- Flu-like symptoms: Fever, asthenia, anorexia, headache, cough, chills, myalgia, 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-treated patients and at a higher incidence in the gemcitabine/carboplatin arm, reported in a randomized trial (Study 1) of gemcitabine 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 occurred in 10% of patients and gemcitabine dose was omitted in 14% of patients in the gemcitabine/carboplatin arm.

Table 7: Adverse Reactions Occurring in >10% of Patients Receiving Gemcitabine with Carboplatin and at Higher Incidence than in Patients Receiving Single Agent Carboplatin [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 1[a]

Adverse Reactions[b]	**Gemcitabine/ 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 Common Toxicity Criteria (CTC) Version 2.0.
[b] Regardless of causality.

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

[Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 1[a]

Laboratory Abnormality[b]	Gemcitabine/ 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 Transfusion[c]	38	-	-	15	-	-
Platelet Transfusion[c]	9	-	-	3	-	-

[a] Grade based on Nutional Cancer Institute CTC Version 2.0.

[b] Regardless of causality.

[c] Percent of patients receiving transfusion. Transfusion 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: leukocyte growth factor (24% and 10%) and erythropoiesis-stimulating agent (7% and 3.9%).

The following clinically relevant, Grade 3 and 4 adverse reactions occurred more frequently in the gemcitabine with 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).

Breast Cancer

Tables 9 and 10 present the incidence of selected adverse reactions and laboratory abnormalities, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the gemcitabine/paclitaxel arm, reported in a randomized trial (Study 2) of gemcitabine with 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)]*. Additional clinically significant adverse reactions, occurring in <10% of patients, are provided following Table 10.

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 adverse reactions (7% versus 5%) and the number of treatment-related deaths (1 patient in each arm) were similar between the two arms.

Table 9: Selected Adverse Reactions Occurring in Patients Receiving Gemcitabine with Paclitaxel and at Higher Incidence than in Patients Receiving Single Agent Paclitaxel [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 2[a]

Adverse Reactions[b]	Gemcitabine/Paclitaxel (N=262)			Paclitaxel (N=259)		
	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] Grade based on National Cancer Institute CTC Version 2.0.
[b] Non-laboratory events were graded only if assessed to be possibly drug-related.

Table 10: Selected Laboratory Abnormalities Occurring in >10% of Patients Receiving Gemcitabine with Paclitaxel and at a Higher Incidence than Patients Receiving Single Agent Paclitaxel [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 2[a]

Laboratory Abnormality[b]	Gemcitabine/ Paclitaxel (N=262)			Paclitaxel (N=259)		
	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] Grade based on National Cancer Institute CTC Version 2.0.
[b] Regardless of causality.

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

Non-Small Cell Lung Cancer

Tables 11 and 12 present the incidence of selected adverse reactions and laboratory abnormalities, occurring in ≥10% of gemcitabine-treated patients and at a higher incidence in the gemcitabine with cisplatin arm, reported in a randomized trial (Study 3) of gemcitabine with cisplatin (n=260) administered in 28-day cycles as compared to cisplatin alone (n=262) in patients receiving first-line treatment for locally advanced or metastatic NSCLC *[see Clinical Studies (14.3)]*.

Patients randomized to gemcitabine with cisplatin received a median of 4 cycles of treatment and those randomized to cisplatin alone 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 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/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 Occurring in ≥10% of Patients Receiving Gemcitabine with Cisplatin and at Higher Incidence than in Patients Receiving Single Agent Cisplatin [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 3[a]

Adverse Reactions[b]	Gemcitabine/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
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] Grade based on National Cancer Institute CTC.
[b] Non-laboratory events were graded only if assessed to be possibly drug-related.
[c] N=217-253; all gemcitabine/cisplatin patients with laboratory or non-laboratory data.
[d] N=213-248; all cisplatin patients with laboratory or non-laboratory data.

Table 12: Selected Laboratory Abnormalities Occurring in >10% of Patients Receiving Gemcitabine with Cisplatin and at Higher Incidence than in Patients Receiving Single Agent Cisplatin [Between Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3-4)] in Study 3[a]

Laboratory Abnormality[b]	Gemcitabine/Cisplatin[c]			Cisplatin[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 Transaminase						
Increased Alkaline	22	2	1	10	1	0
Phosphatase	19	1	0	13	0	0
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=217-253; all gemcitabine/cisplatin patients with laboratory or non-laboratory data.
[d] N=213-248; 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-treated patients and at a higher incidence in the gemcitabine with cisplatin arm, reported in a randomized trial (Study 4) of gemcitabine 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/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/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 WHO.
[b] Non-laboratory events were graded only if assessed to be possibly drug-related. Pain data were not collected.
[c] N=67-69; all gemcitabine/cisplatin patients with laboratory or non-laboratory data.

[d] N=57-63; 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/Cisplatin[c]			Etoposide/Cisplatin[d]		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	88	22	0	77	13	2
Neutropenia	88	36	28	87	20	56
Thrombocytopenia	81	39	16	45	8	5
RBC Transfusion[e]	29	-	-	21	-	-
Platelet Transfusion[e]	3	-	-	8	-	-
Hepatic						
Increased Alkaline Phosphatase	16	0	0	11	0	0
Increased ALT	6	0	0	12	0	0
Increased AST	3	0	0	11	0	0
Renal						
Hematuria	22	0	0	10	0	0
Proteinuria	12	0	0	5	0	0
Increased BUN	6	0	0	4	0	0
Increased Creatinine	2	0	0	2	0	0

[a] Grade based on criteria from WHO.
[b] Regardless of causality.
[c] N=67-69; all gemcitabine/cisplatin patients with laboratory or non-laboratory data.
[d] N=57-63; all etoposide/cisplatin patients with laboratory or non-laboratory data.
[e] Percent of patients receiving transfusions. WHO Grading scale not applicable to proportion patients with transfusions.

6.2 Postmarketing 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.

Blood and Lymphatic System: TMA

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

Vascular : Peripheral vasculitis, gangrene capillary leak syndrome

Skin: Cellulitis, pseudocellulitis, severe skin reactions, including desquamation and bullous skin eruptions.

Hepatic: Hepatic failure, hepatic veno-occlusive disease

Pulmonary: Interstitial pneumonitis, pulmonary fibrosis, pulmonary eosinophilia, pulmonary edema, 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 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 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 Specific Populations (8.3)]*.

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

Data

Animal Data

Gemcitabine is embryotoxic in mice. Daily dosing of gemcitabine to pregnant mice increased the incidence of fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day [about 0.005 times the 1000 mg/m^2 clinical dose based on body surface area (BSA)]. Gemcitabine is 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 (about 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 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, advise women not to breastfeed during treatment with Gemcitabine 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 Injection *[see Use in Specific Populations (8.1)]*.

Contraception

Gemcitabine 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 Injection and for 6 months after the final dose.

Males

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

Infertility

Males

Based on animal studies, gemcitabine 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 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, 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, no overall differences in safety were observed between patients aged 65 and older and younger patients, with the exception of a higher rate of Grade 3-4 thrombocytopenia in older patients as compared to younger patients.

In a randomized trial in women with ovarian cancer (Study 1), 175 women received gemcitabine 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 clearance is affected by age; however, there are no recommended dose adjustments based on patients' age *[see Clinical Pharmacology (12.3)]*.

8.6 Gender

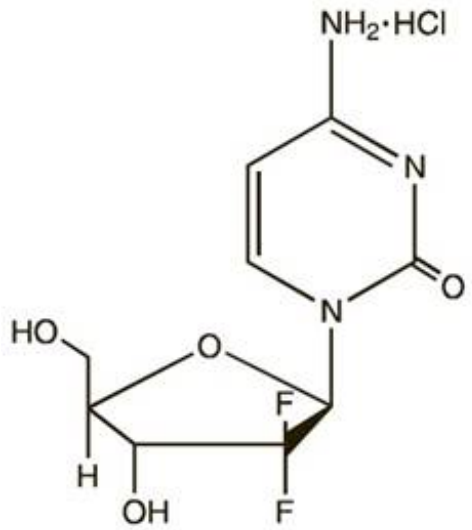
Gemcitabine clearance is decreased in females *[see Clinical Pharmacology (12.3)]*. In single agent studies of gemcitabine, women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3-4 neutropenia and thrombocytopenia *[see Dosage and Administration (2.1, 2.2, 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. The chemical name of gemcitabine HCl, USP is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (β-isomer).The structural formula is as follows:



Gemcitabine HCl, USP is a white to off-white solid with a molecular formula of $C_9H_{11}F_2N_3O_4$ • HCl and a molecular weight of 299.66 g/mol. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

Gemcitabine Injection is a sterile solution in single-dose vials for intravenous use. Each vial contains 200 mg, 1 g, or 2 g of gemcitabine equivalent to 227.7 mg, 1.139 g, or 2.227 g of gemcitabine HCl, USP. Each mL contains 38 mg of gemcitabine free base in Water for Injection equivalent to 43.27 mg of gemcitabine HCl, USP. 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 dose varied from 500 mg/m^2 to 3600 mg/m2.

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 (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2´-deoxy-2´,2´-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

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.

Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and for long infusions varied from 245 to 638 minutes, depending on age and sex, reflecting a greatly increased volume of distribution with longer infusions.

Male and Female Patients

Females have lower clearance and longer half-lives than male patients as described in Table 15.

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

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

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

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/m2 on Days 1 and 8) and cisplatin (75 mg/m2 on Day 1) were administered in patients with NSCLC, the clearance of gemcitabine on Day 1 was 128 L/hr/m2 and on Day 8 was 107 L/hr/m2. Data from patients with NSCLC 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.

Data from patients with metastatic breast cancer shows that 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.

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 intraperitoneal doses of 0.5 mg/kg/day (about 1/700 the 1000 mg/m^2 clinical dose based on 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/m2 clinical dose based on BSA).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

The efficacy of gemcitabine 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 1000 mg/m^{2}on Days 1 and 8 of each 21-day cycle with carboplatin AUC 4 on Day 1 after gemcitabine 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 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 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/Carboplatin (N=178)	**Carboplatin (N=178)**
Median age, years Range	59 36 to 78	58 21 to 81
Baseline ECOG performance status 0-1[a]	94%	95%
Disease Status Evaluable Bidimensionally measurable	8% 92%	3% 96%
Platinum-free intervalb 6-12 months >12 months	40% 59%	40% 60%
First-line therapy Platinum-taxane combination Platinum-	70% 29%	71% 28%

non-taxane combination Platinum monotherapy	1%	1%

[a] 5 patients on the gemcitabine/carboplatin arm and 4 patients on the carboplatin arm had no baseline Eastern Cooperative Oncology Group (ECOG) performance status.

[b] 2 patients on the gemcitabine/carboplatin arm and 1 on the carboplatin arm had a platinum-free interval < 6 months.

Table 17: Efficacy Results in Study 1

Efficacy parameter	**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 Review	47.2	30.9
p=value[c]	0.0016	
CR[d] PR+PRNM[e]	14.6% 32.6%	6.2% 24.7%
Overall Response Rate by Independent Review[f]	46.3%	35.6%
p=value[c]	p=0.11	
CR[d] PR+PRNM[e]	9.1% 37.2%	4.0% 31.7%

[a] CI= confidence interval.

[b] Log rank, unadjusted.

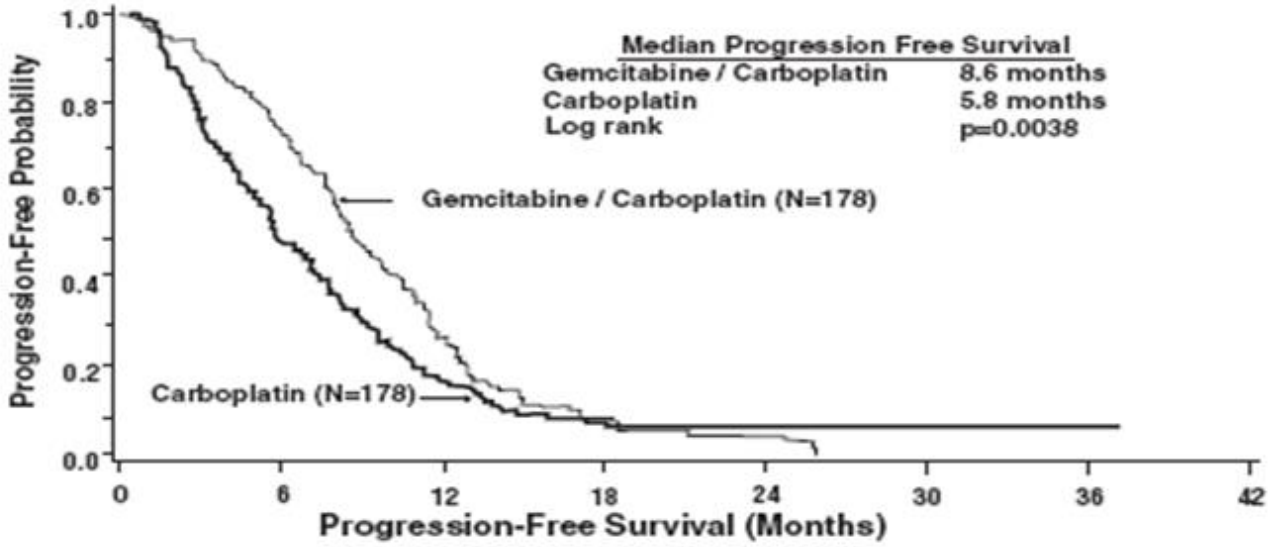
[c] Chi square.

[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 for Progression-Free Survival in Study 1



14.2 Breast Cancer

The efficacy of gemcitabine was evaluated in a multinational, randomized, open-label trial 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 gemcitabine 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 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 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/Paclitaxel (N = 267)	**Paclitaxel (N = 262)**
Median age, years Range	53 26 to 83	52 26 to 75
Metastatic disease	97%	97%
Baseline KPS[a] ≥90	70%	74%
Number of tumor sites 1-2 ≥3	 57% 43%	 59% 41%
Visceral disease	73%	73%
Prior anthracycline	97%	96%

[a] Karnofsky Performance Status.

Table 19: Efficacy Results in Study 2

Efficacy Parameter	**Gemcitabine/Paclitaxel (N=267)**	**Paclitaxel (N=262)**
Time to Documented Disease		

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[b] (95% CI)	40.8% (34.9, 46.7)	22.1% (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 was evaluated in two randomized, multicenter trials.

Study 3: 28-Day Schedule

A multinational, randomized trial (Study 3) compared gemcitabine 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 1000 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m^2 on Day 1 after gemcitabine 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 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 gemcitabine 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 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 with cisplatin arm versus 7 months for the etoposide with cisplatin arm. Median time to disease progression for the gemcitabine with cisplatin arm was 5 months compared to 4.1 months on the etoposide with cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the gemcitabine with cisplatin arm was 33% compared to 14% on the etoposide with cisplatin arm (Fisher's Exact p=0.01, two-sided).

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

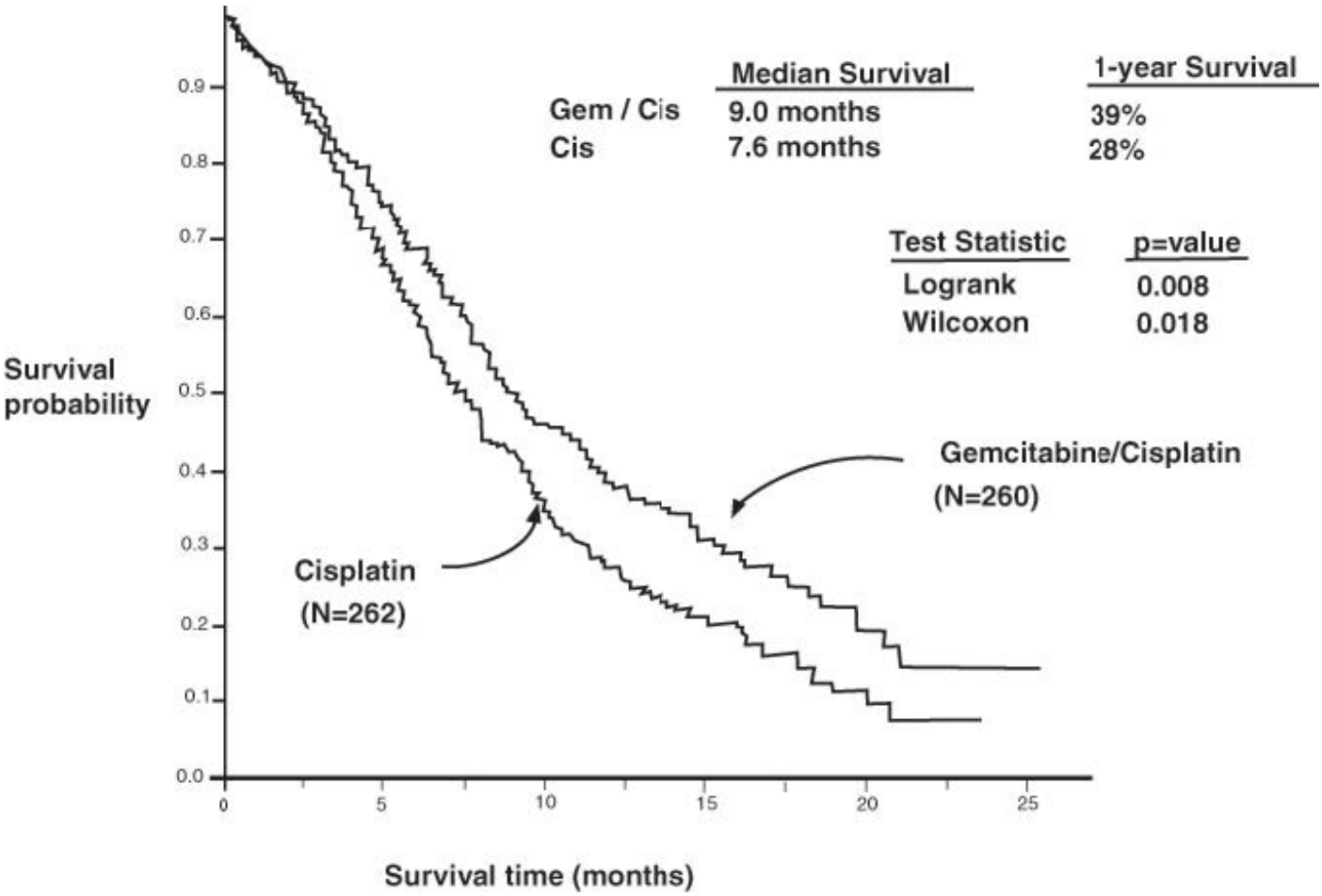


Table 20: Baseline Demographics and Clinical Characteristics for Studies 3 and 4

Trial	28-day Schedule (Study 3)		21-day Schedule(Study 4)	
	Gemcitabine/ Cisplatin (N=260)	Cisplatin (N=262)	Gemcitabine/ Cisplatin (N=69)	Etoposide/ Cisplatin (N=66)
Male	70%	71%	93%	92%
Median age, years	62	63	58	60
Range	36 to 88	35 to 79	33 to 76	35 to 75
Stage IIIA	7%	7%	N/A[a]	N/A[a]
Stage IIIB	26%	23%	48%	52%
Stage IV	67%	70%	52%	49%
Baseline KPS[b] 70 to 80	41%	44%	45%	52%
Baseline KPS[b] 90 to 100	57%	55%	55%	49%

[a] N/A Not applicable.

[b] Karnofsky Performance Status.

Table 21: Efficacy Results for Studies 3 and 4

Trial	28-day Schedule (Study 3)		21-day Schedule(Study 4)	
Efficacy Parameter	Gemcitabine/Cisplatin (N=260)	Cisplatin (N=262)	Gemcitabine/ 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[b]	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-valiue two-side Fisher's Extract test for difference in binomial proportions; log rank test for time-to-event analyses.

14.4 Pancreatic Cancer

The 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 fluorouracil or a fluorouracil-containing regimen. In Study 5, patients were randomized to receive either gemcitabine 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 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.

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:

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

OR

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

Study 5 enrolled 126 patients. Demographics and baseline characteristics were similar between the arms (Table 22).

The efficacy results are shown in Table 23 and Figure 4. Patients treated with gemcitabine had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to those randomized to receive fluorouracil. No confirmed objective tumor responses were observed in either treatment arm.

Table 22: Baseline Demographics and Clinical Characteristics for Study 5

	Gemcitabine (N=63)	**Fluorouracil (N=63)**
Male	54%	54%
Median age	62 years	61 years
Range	37 to 79	36 to 77
Stage IV disease	71%	76%
Baseline KPS[a] ≤70	70%	68%

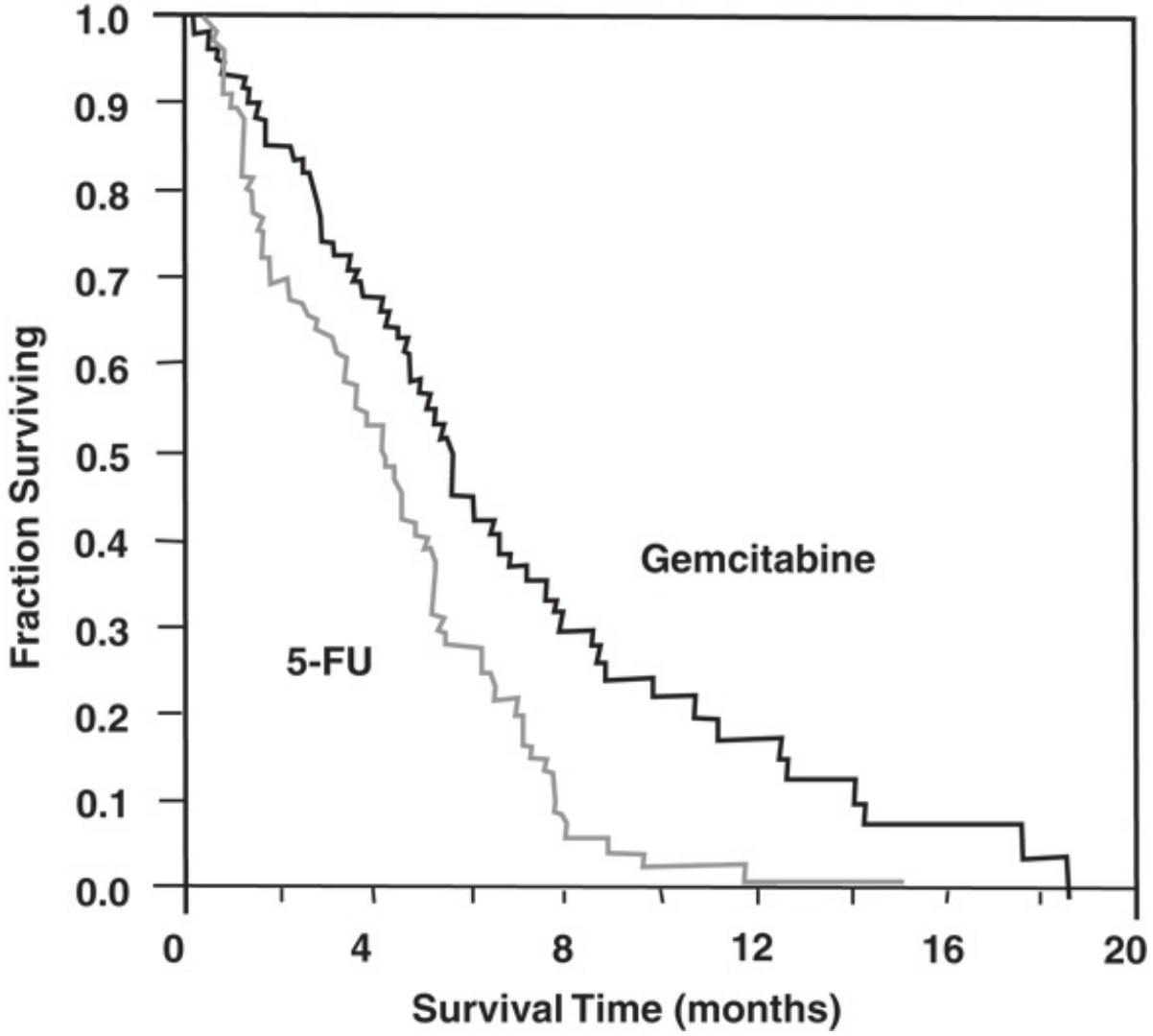
[a] Karnofsky Performance Status.

Table 23: Efficacy Results in Study 5

Efficacy Parameter	**Gemcitabine (N=63)**	**Fluorouracil (N=63)**
Clinical Benefit Response	22.2%	4.8%
p-value[a]	p=0.004	
Overall Survival Median (95% CI) in months	5.7 (4.7, 6.9)	4.2 (3.1, 5.1)
p-value[a]	p=0.0009	
Time to Disease Progression Median (95% CI) in months	2.1 (1.9, 3.4)	0.9 (0.9, 1.1)
p-value[a]	p=0.0013	

[a] 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 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 Injection appears as a clear and colorless to light straw-colored solution. It is available in sterile single-dose vials individually packaged in a carton as follows:

- 200 mg/5.26 mL (38 mg/mL), sterile solution in a single-dose glass vial per package, NDC 50742-498-05
- 1 g/26.3 mL (38 mg/mL), sterile solution in a single-dose glass vial per package, NDC 50742-496-26
- 2 g/52.6 mL (38 mg/mL), sterile solution in a single-dose glass vial per package, NDC 50742-497-53

Unopened vials of Gemcitabine Injection are stable until the expiration date indicated on the package when stored at 2° to 8°C (36° to 46°F). Do not freeze.

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

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 Injection can cause fetal harm. 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 treatment with Gemcitabine 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 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 Injection *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Manufactured for:

Ingenus Pharmaceuticals, LLC

Orlando, FL 32839-6408

Made in Switzerland.

Revised: 9/2019

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

1097-0002

NDC 50742-498-05

Gemcitabine Injection

200 mg/5.26 mL (38 mg/mL)

For Intravenous Infusion Only

Must Be Diluted Before Use

5.26 mL Single-Dose Vial

Discard Unused Portion

Caution: Cytotoxic Agent

℞ Only

ingenus

Each vial contains:
200 mg gemcitabine (equivalent to 227.7 mg gemcitabine hydrochloride, USP) and Water for Injection, USP. Hydrochloric acid, NF and/or sodium hydroxide, NF may have been added to adjust pH.

For Dosing and Administration:
See package insert.
Store at 2° to 8°C (36° to 46°F).

Manufactured for:
Ingenus Pharmaceuticals, LLC
Orlando, FL 32839-6408
Made in Switzerland

498-05 v2/09-2019

N 3 50742 49805 5

Lot No.:

Exp. Date:

Vial Label - 200 mg/5.26 mL

1098-0002

NDC 50742-496-26

Gemcitabine Injection

1 g/26.3 mL (38 mg/mL)

For Intravenous Infusion Only

Must Be Diluted Before Use

26.3 mL Single-Dose Vial

Discard Unused Portion

Caution: Cytotoxic Agent

℞ Only

ingenus

Each vial contains:
1 g gemcitabine (equivalent to 1.139 g gemcitabine hydrochloride, USP) and Water for Injection, USP. Hydrochloric acid, NF and/or sodium hydroxide, NF may have been added to adjust pH.

For Dosing and Administration:
See package insert.

Store at 2° to 8°C (36° to 46°F).

Manufactured for:
Ingenus Pharmaceuticals, LLC
Orlando, FL 32839-6408

Made in Switzerland

496-26 v2/09-2019

N 3 50742 49626 6

Lot No.:

Exp. Date:

Vial Label - 1 g/ 26.3 mL

1099-0002

NDC 50742-497-53

Gemcitabine Injection

2 g/52.6 mL (38 mg/mL)

For Intravenous Infusion Only

Must Be Diluted Before Use

52.6 mL Single-Dose Vial

Discard Unused Portion

Caution: Cytotoxic Agent

℞ Only

ingenus

Each vial contains:
2 g gemcitabine (equivalent to 2.227 g gemcitabine hydrochloride, USP) and Water for Injection, USP. Hydrochloric acid, NF and/or sodium hydroxide, NF may have been added to adjust pH.

For Dosing and Administration:
See package insert.

Store at 2° to 8°C (36° to 46°F).

Manufactured for:
Ingenus Pharmaceuticals, LLC
Orlando, FL 32839-6408

Made in Switzerland

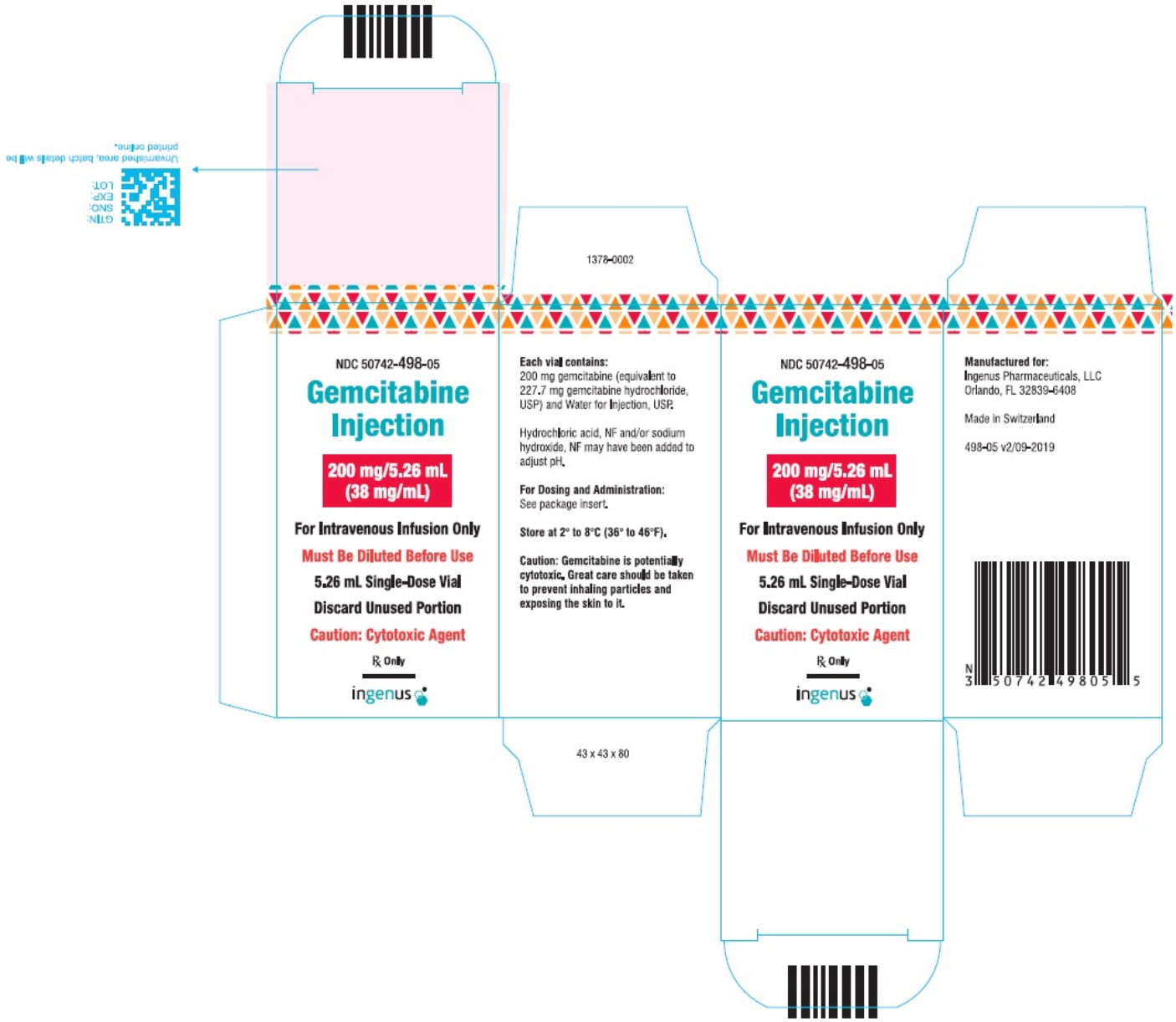
497-53 v2/09-2019

N 3 50742 49753 9

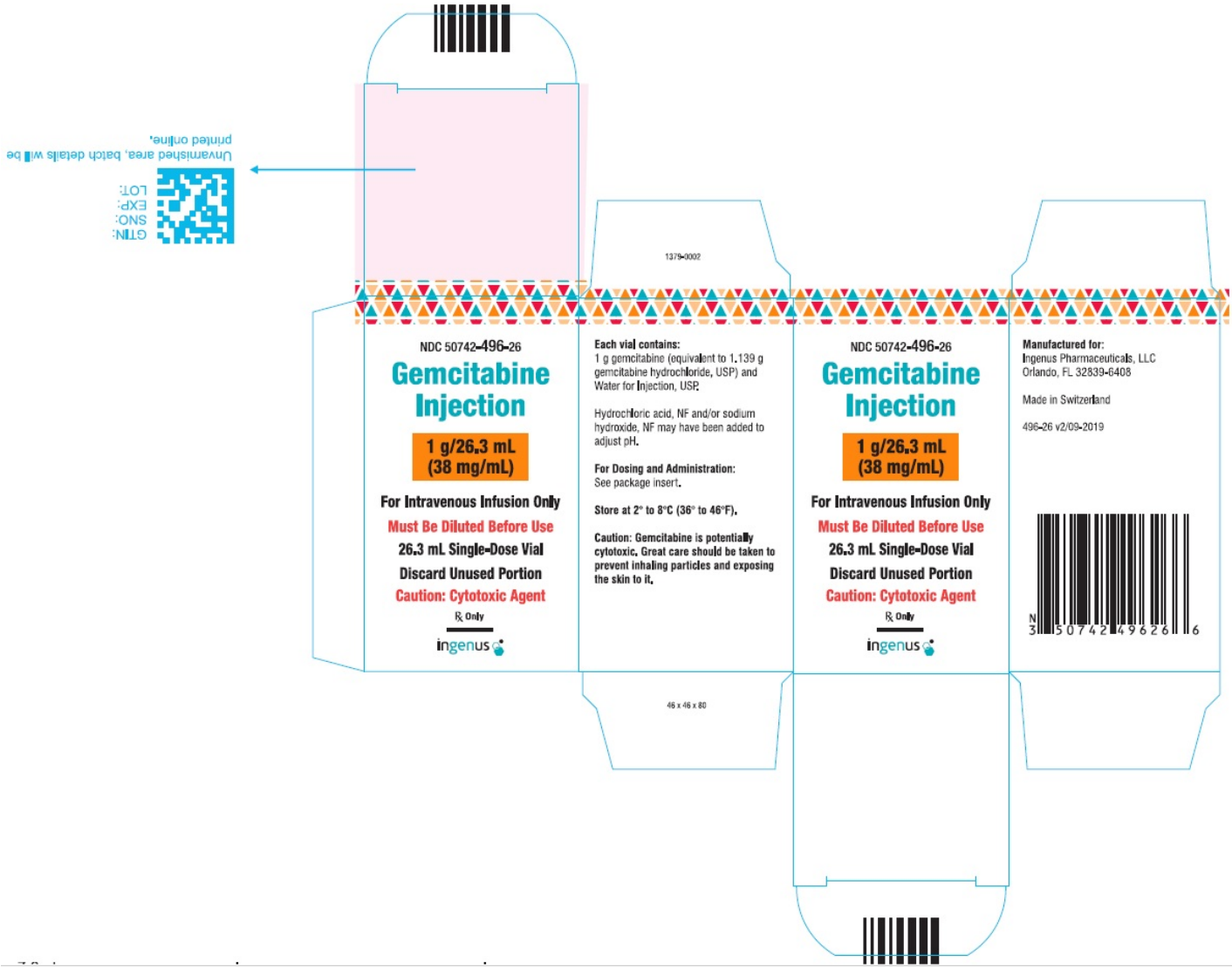
Lot No.:

Exp. Date:

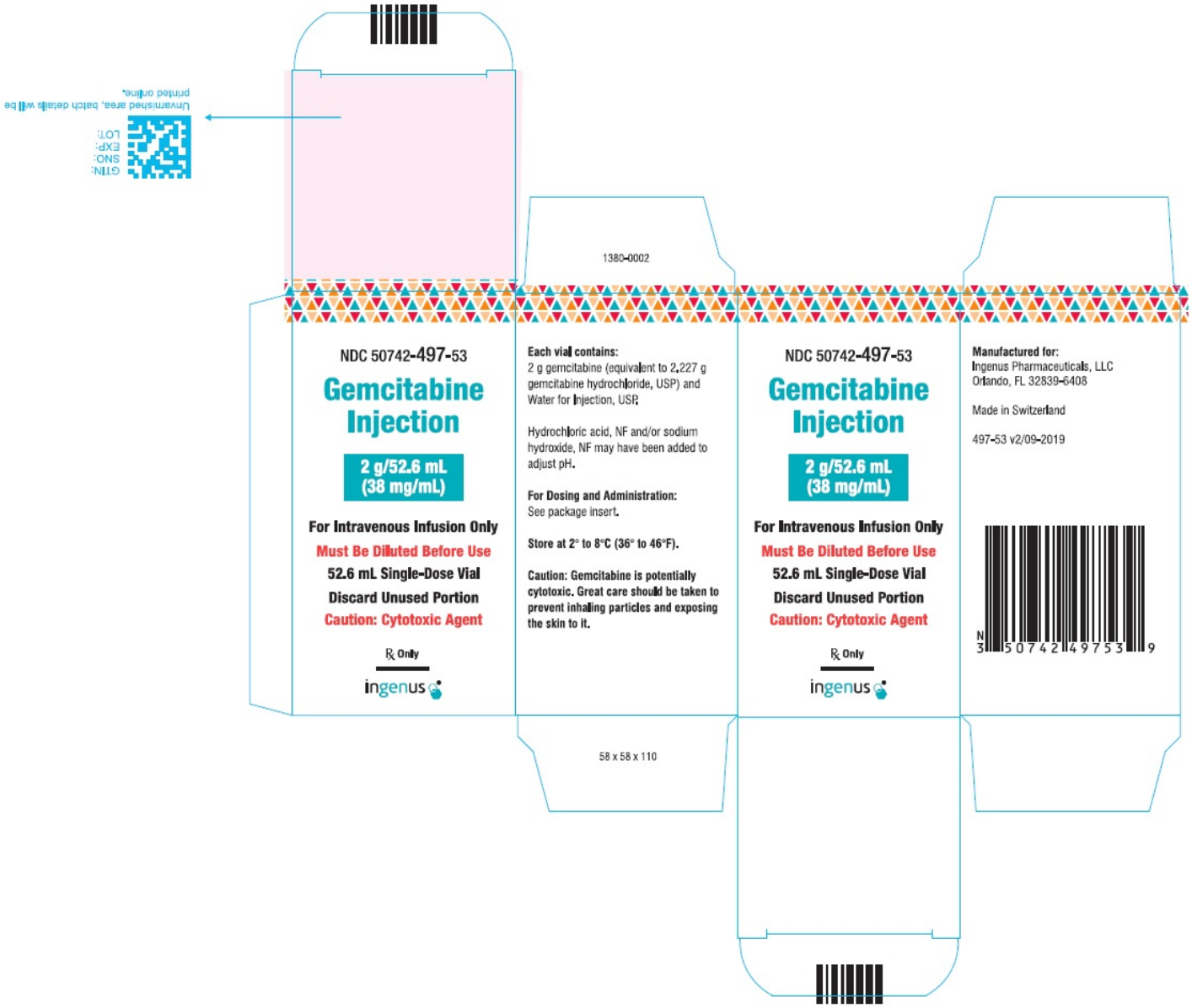
Vial Label - 2 g/ 52.6 mL



Carton Label - 200 mg/5.26 mL



Carton Label - 1 g/26.3 mL



Carton Label - 2 g/52.6 mL

GEMCITABINE

gemcitabine injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-498
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GEMCITABINE HYDROCHLORIDE (UNII: U347PV74IL) (GEMCITABINE - UNII:B76N6SBZ8R)	GEMCITABINE	38 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength

SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-498-05	1 in 1 CARTON	02/26/2019	
1		5.26 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210383	02/26/2019	

GEMCITABINE

gemcitabine injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-496
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GEMCITABINE HYDROCHLORIDE (UNII: U347PV74IL) (GEMCITABINE - UNII:B76N6SBZ8R)	GEMCITABINE	38 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-496-26	1 in 1 CARTON	02/26/2019	
1		26.3 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210383	02/26/2019	

GEMCITABINE

gemcitabine injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-497
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GEMCITABINE HYDROCHLORIDE (UNII: U347PV74IL) (GEMCITABINE - UNII:B76N6SBZ8R)	GEMCITABINE	38 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
HYDROCHLORIC ACID (UNII: QTT17582CB)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-497-53	1 in 1 CARTON	02/26/2019	
1		52.6 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA210383	02/26/2019	

Labeler - Ingenus Pharmaceuticals, LLC (833250017)

Registrant - Novast Laboratories, Ltd. (527695995)

Establishment

Name	Address	ID/FEI	Business Operations
Ingenus			MANUFACTURE(50742-498, 50742-496, 50742-497) , ANALYSIS(50742-498, 50742-496,

Pharmaceuticals GmbH		482730327	50742-497) , LABEL(50742-498, 50742-496, 50742-497) , PACK(50742-498, 50742-496, 50742-497) , STERILIZE(50742-498, 50742-496, 50742-497)