

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

INDICATIONS AND USAGE

Gemcitabine for Injection is a nucleoside metabolic inhibitor indicated for:

- Ovarian cancer in combination with carboplatin (1.1)
- Breast cancer in combination with paclitaxel (1.2)
- Non-small cell lung cancer in combination with cisplatin (1.3)
- Pancreatic cancer as a single-agent (1.4)

DOSEAGE AND ADMINISTRATION

Gemcitabine for Injection is for intravenous use only.

- Ovarian cancer: 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.1)
- Breast cancer: 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.2)
- Non-small cell lung cancer: 4-week schedule, 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle: 3-week schedule: 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle (2.3)
- Pancreatic cancer: 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks (2.4)
- Dose Reductions or discontinuation may be needed based on toxicities (2.1-2.4)

DOSEAGE FORMS AND STRENGTHS

- 200 mg vial for injection (3)
- 1 g vial for injection (3)
- 2 g vial for injection (3)

CONTRAINDICATIONS

Patients with a known hypersensitivity to gemcitabine (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

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

1.3 Non-Small Cell Lung Cancer

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

1.4 Pancreatic Cancer

Gemcitabine for 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 for Injection is indicated for patients previously treated with 5-FU.

2 DOSEAGE AND ADMINISTRATION

Gemcitabine for Injection is for intravenous use only. Gemcitabine for Injection may be administered on an outpatient basis.

2.1 Ovarian Cancer

Gemcitabine for Injection should be administered intravenously at a dose of 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after Gemcitabine for Injection administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10⁹/L and a platelet count ≥100,000 x 10⁹/L prior to each cycle.

Dose Modifications

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

Table 1: Day 8 Dosage Reduction Guidelines for Gemcitabine for Injection in Combination with Carboplatin			
Absolute granulocyte count (x 10 ⁹ /L)	Platelet count (x 10 ⁹ /L)	% of full dose	
≥1500	and	≥100,000	100
1000-1499	and/or	75,000-99,999	50
<1000	and/or	<75,000	Hold

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

Dose adjustment for Gemcitabine for Injection in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of Gemcitabine for Injection in subsequent cycles should be reduced to 800 mg/m² on Days 1 and 8 in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10⁹/L for more than 5 days
- Absolute granulocyte count <100 x 10⁹/L for more than 3 days
- Febrie neutropenia
- Platelets <25,000 x 10⁹/L
- Cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction, for the subsequent cycle, Gemcitabine for Injection should be given on Day 1 only at 800 mg/m².

2.2 Breast Cancer

Gemcitabine for Injection should be administered intravenously at a dose of 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m² on Day 1 as a 3-hour intravenous infusion before Gemcitabine for Injection administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10⁹/L and a platelet count ≥100,000 x 10⁹/L prior to each cycle.

Dose Modifications

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

Table 2: Day 8 Dosage Reduction Guidelines for Gemcitabine for Injection in Combination with Paclitaxel			
Absolute granulocyte count (x 10 ⁹ /L)	Platelet count (x 10 ⁹ /L)	% of full dose	
≥1200	and	>75,000	100
1000-1199	or	50,000-75,000	75
700-999	and	≥50,000	50
<700	or	<50,000	Hold

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

2.3 Non-Small Cell Lung Cancer

Two schedules have been investigated and the optimum schedule has not been determined [see Clinical Studies (14.3)]. With the 4-week schedule, Gemcitabine for Injection should be administered intravenously at 1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m² on Day 1 after the infusion of Gemcitabine for Injection. With the 3-week schedule, Gemcitabine for Injection should be administered intravenously at 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100 mg/m² should be administered intravenously after the infusion of Gemcitabine for Injection on Day 1. See prescribing information for cisplatin administration and hydration guidelines.

Dose Modifications

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

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

2.4 Pancreatic Cancer

Gemcitabine for Injection should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

Dose Modifications

Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient [see Warnings and Precautions (5.2)]. Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]. Patients receiving Gemcitabine for Injection should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3.

Table 3: Dosage Reduction Guidelines			
Absolute granulocyte count (x 10 ⁹ /L)	Platelet count (x 10 ⁹ /L)	% of full dose	
≥1000	and	≥100,000	100
500-999	or	50,000-99,999	75
<500	or	<50,000	Hold

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

Patients treated with Gemcitabine for Injection who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 10⁹/L and 100,000 x 10⁹/L, respectively, and if non-hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemcitabine for Injection at the increased dose, the dose for the next cycle can be further increased by 20%, provided again that the AGC and platelet nadirs exceed 1500 x 10⁹/L and 100,000 x 10⁹/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

2.5 Preparation and Administration Precautions

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

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

2.6 Preparation for Intravenous Infusion Administration

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

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial or 50 mL of 0.9% Sodium Chloride Injection to the 2-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial or 2.6 mL for the 2-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL or 52.6 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g or 2 g of gemcitabine, respectively. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

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

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

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

3 DOSEAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

Patients receiving therapy with Gemcitabine for Injection should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.

5.1 Infusion Time

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

5.2 Hematology

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

5.3 Pulmonary

Pulmonary toxicity has been reported with the use of Gemcitabine for Injection. In cases of severe lung toxicity, Gemcitabine for Injection therapy should be discontinued immediately and appropriate supportive care measures instituted [see Adverse Reactions (6.1 and 6.2)].

5.4 Renal

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine for Injection. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been reported. The majority of the cases of renal failure leading to death were due to HUS [see Adverse Reactions (6.1 and 6.2)].

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

5.5 Hepatic

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

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

5.6 Pregnancy

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

5.7 Laboratory Tests

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

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

5.8 Radiation Therapy

A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and non-concurrent use of Gemcitabine for Injection.

Non-concurrent (given >7 days apart). Analysis of the data does not indicate enhanced toxicity when Gemcitabine for Injection is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that Gemcitabine for Injection can be started after the acute effects of radiation have resolved or at least one week after radiation.

Concurrent (given together or <7 days apart). Pre-clinical and clinical studies have shown that Gemcitabine for Injection has radiosensitizing activity. Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of Gemcitabine for Injection, frequency of Gemcitabine for Injection, dose of radiation, radiation planning technique, the target tissue, and target volume. In a single trial, where Gemcitabine for Injection at a dose of 1000 mg/m² was administered concurrently for up to 6 consecutive weeks with therapeutic thoracic radiation to patients with non-small cell lung cancer, significant toxicity in the form of severe, and potentially life-threatening mucositis, especially esophagitis and pneumonitis was observed, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4795 cm³]. Subsequent studies have been reported and suggest that Gemcitabine for Injection administered at lower doses with concurrent radiotherapy has predictable and less severe toxicity. However, the optimum regimen for safe administration of Gemcitabine for Injection with therapeutic doses of radiation has not yet been determined in all tumor types.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

Single-Agent Use:

Myelosuppression is the principal dose-limiting toxicity with Gemcitabine for Injection therapy. Dosage adjustments for hematologic toxicity are frequently needed [see Dosage and Administration (2.1, 2.2, 2.3, and 2.4)].

The data in Table 4 are based on 979 patients receiving Gemcitabine for Injection as a single-agent administered weekly as a 30-minute infusion for treatment of a wide variety of malignancies. The Gemcitabine for Injection starting doses ranged from 800 to 1250 mg/m². Data are also shown for the subset of patients with pancreatic cancer treated in 5 clinical studies. The frequency of all grades and severe (WHO Grade 3 or 4) adverse reactions were generally similar in the single-agent safety database of 979 patients and the subset of patients with pancreatic cancer. Adverse reactions reported in the single-agent safety database resulted in discontinuation of Gemcitabine for Injection therapy in about 10% of patients. In the comparative trial in pancreatic cancer, the discontinuation rate for adverse reactions was 14.3% for the Gemcitabine for Injection arm and 4.8% for the 5-FU arm. All WHO-graded laboratory adverse reactions are listed in Table 4, regardless of causality. Non-laboratory adverse reactions listed in Table 4 or discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific adverse reactions under the Renal, Pulmonary and Infection categories.

Table 4: Selected WHO-Graded Adverse Reactions in Patients Receiving Single-Agent Gemcitabine for Injection WHO Grades (% Incidence) ^a							
	All Patients ^a			Pancreatic Cancer Patients ^a			Discontinuations (%) ^a
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Patients
Laboratory^b							
Hematologic							
Anemia	68	7	1	73	8	2	<1
Leukopenia	62	9	<1	64	8	1	<1
Neutropenia	63	19	6	61	17	7	-
Thrombocytopenia	24	4	1	36	7	<1	<1
Hepatic							
ALT	68	8	2	72	10	1	<1
AST	67	6	2	78	12	5	
Alkaline Phosphatase	55	7	2	77	16	4	
Bilirubin	13	2	<1	26	6	2	
Renal							
Proteinuria	45	<1	0	32	<1	0	<1
Hematuria	35	<1	0	23	0	0	
BUN	16	0	0	15	0	0	
Creatinine	8	<1	0	6	0	0	
Non-laboratory^b							
Nausea and Vomiting	69	13	1	71	10	2	<1
Fever	41	2	0	38	2	0	<1
Rash	30	<1	0	28	<1	0	<1
Dyspnea	23	3	<1	10	0	<1	<1
Diarrhea	19	1	0	30	3	0	0
Hemorrhage	17	<1	<1	4	2	<1	<1
Infection	16	1	<1	10	2	<1	<1
Alopecia	15	<1	0	16	0	0	0
Stomatitis	11	<1	0	10	<1	0	<1
Somnolence	11	<1	<1	11	2	<1	<1
Paresthesias	10	<1	0	10	<1	0	0

The following are the clinically relevant adverse reactions that occurred in >1% and <10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse reactions (Gemcitabine for Injection plus paclitaxel versus paclitaxel): febrile neutropenia (5.0% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity (0 versus 0.8%).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

Combination Use in Ovarian Cancer:

In the Gemcitabine for Injection plus carboplatin versus carboplatin study, dose reductions occurred with 10.4% of Gemcitabine for Injections and 1.8% of carboplatin injections on the combination arm, versus 3.8% on the carboplatin alone arm. On the combination arm, 13.7% of Gemcitabine for Injection doses were omitted and 0.2% of carboplatin doses were omitted, compared to 0% of carboplatin doses on the carboplatin alone arm. There were no differences in discontinuations due to adverse reactions between arms (10.9% versus 9.8%, respectively).

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

Table 8: Adverse Reactions From Comparative Trial of Gemcitabine for Injection Plus Carboplatin Versus Single-Agent Carboplatin in Ovarian Cancer*

	CTC Grades (% Incidence)					
	Gemcitabine for Injection plus Carboplatin (N=175)			Carboplatin (N=174)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory^a						
Hematology						
Neutropenia	90	42	29	58	11	1
Anemia	86	22	6	75	9	2
Leukopenia	86	48	5	70	6	<1
Thrombocytopenia	78	30	5	57	10	1
RBC Transfusions ^c	38			15		
Platelet Transfusions ^c	9			3		
Non-laboratory^b						
Nausea	69	6	0	61	3	0
Allopexia	49	0	0	17	0	0
Vomiting	46	6	0	36	2	<1
Constipation	42	6	1	37	3	0
Fatigue	40	3	<1	32	5	0
Neuropathy-sensory	29	1	0	27	2	0
Diarrhea	25	3	0	14	<1	0
Stomatitis/pharyngitis	22	<1	0	13	0	0
Anorexia	16	1	0	13	0	0

^a Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%).

^b Regardless of causality.

^c Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red blood cells and whole blood.

In addition to blood product transfusions as listed in Table 8, myelosuppression was also managed with hematopoietic factors. These agents were administered more frequently with combination therapy than with monotherapy (granulocyte growth factors: 23.6% and 10.1%, respectively; erythropoietic agents: 7.3% and 3.9%, respectively).

The following are the clinically relevant adverse reactions, regardless of causality, that occurred in >1% and <10% (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse reactions (Gemcitabine for Injection plus carboplatin versus carboplatin): AST or ALT elevation (0 versus 1.2%), dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), hemorrhagic event (2.3% versus 1.1%), hypersensitivity reaction (2.3% versus 2.9%), motor neuropathy (1.1% versus 0.6%), and rash/desquamation (0.6% versus 0).

No differences in the incidence of laboratory and non-laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Gemcitabine for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions have occurred after Gemcitabine for Injection single-agent use and Gemcitabine for Injection in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemcitabine for Injection.

Cardiovascular - Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemcitabine for Injection. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.

Vascular Disorders - Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.

Skin - Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported. Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.

Hepatic - Increased liver function tests including elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemcitabine for Injection alone or in combination with other potentially hepatotoxic drugs. Hepatic vein-occlusive disease has been reported.

Pulmonary - Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of Gemcitabine for Injection administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemcitabine for Injection dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.

Renal - Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine for Injection. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.

Injury, Poisoning, and Procedural Complications - Radiation recall reactions have been reported. [see Warnings and Precautions (5.8)]

7 DRUG INTERACTIONS

No specific drug interaction studies have been conducted. Information is available on the pharmacodynamics and pharmacokinetics of Gemcitabine for Injection in combination with cisplatin, paclitaxel, or carboplatin. [see Clinical Pharmacology (12.2 and 12.3)]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Gemcitabine for Injection can cause fetal harm when administered to a pregnant woman. Based on its mechanism of action, Gemcitabine for Injection is expected to result in adverse reproductive effects. There are no adequate and well-controlled studies of Gemcitabine for Injection in pregnant women.

Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m² basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [see Warnings and Precautions (5.6)]

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of Gemcitabine for Injection in pediatric patients has not been established. Gemcitabine for Injection was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Gemcitabine for Injection was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

8.5 Geriatric Use

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

8.6 Renal

Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine for Injection. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been reported. The majority of the cases of renal failure leading to death were due to HUS [see Adverse Reactions (6.1 and 6.2)].

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

8.7 Hepatic

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

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

8.8 Gender

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

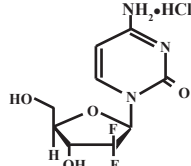
10 OVERDOSAGE

There is no known antidote for overdoses of Gemcitabine for Injection. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m² was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

11 DESCRIPTION

Gemcitabine for Injection, USP is a nucleoside metabolite inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer).

The structural formula is as follows:



The empirical formula for gemcitabine HCl is C₈H₁₁F₂N₃O₃ • HCl. It has a molecular weight of 299.66.

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleosides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total Gemcitabine for Injection dose varied from 500 to 3600 mg/m².

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m² following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m².

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

Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m²/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2', 2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Excretion

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 9 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

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

Age	Clearance Men (L/hr/m ²)	Clearance Women (L/hr/m ²)	Half-Life* Men (min)	Half-Life* 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

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

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

Drug Interactions

When Gemcitabine for Injection (1250 mg/m² on Days 1 and 8) and cisplatin (75 mg/m² on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m² and on Day 8 was 107 L/hr/m². The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m² with a corresponding half-life of 134 hours [see Drug Interactions (7)]. Analysis of data from metastatic breast cancer patients shows that, on average, Gemcitabine 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 for Injection. Data from NSCLC patients demonstrate that Gemcitabine for Injection and carboplatin given in combination does not alter the pharmacokinetics of Gemcitabine for Injection or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of Gemcitabine for Injection have not been conducted. Gemcitabine induced forward mutations *in vitro* in a mouse lymphoma (L5178Y) assay and was clastogenic in an *in vivo* mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, *in vitro* sister chromatid exchange, and *in vitro* chromosomal aberration assays, and did not cause unscheduled DNA synthesis *in vitro*. Gemcitabine IP doses of 0.5 mg/kg/day (about 1/700 the human dose on a

mg/m² basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day administered intravenously (about 1/200 the human dose on a mg/m² basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

Gemcitabine for Injection was studied in a randomized Phase 3 study of 356 patients with advanced ovarian cancer that had relapsed at least 6 months after first-line platinum-based therapy. Patients were randomized to receive either Gemcitabine for Injection 1000 mg/m² on Days 1 and 8 of a 21-day cycle and carboplatin AUC 4 administered after Gemcitabine for Injection on Day 1 of each cycle or single-agent carboplatin AUC 5 administered on Day 1 of each 21-day cycle as the control arm. The primary endpoint of this study was progression free survival (PFS).

Patient characteristics are shown in Table 10. The addition of Gemcitabine for Injection to carboplatin resulted in statistically significant improvement in PFS and overall response rate as shown in Table 11 and Figure 1. Approximately 75% of patients in each arm received post study chemotherapy. Only 13 of 120 patients with documented post study chemotherapy regimen in the carboplatin arm received Gemcitabine for Injection after progression. There was not a significant difference in overall survival between arms.

Table 10: Gemcitabine for Injection Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Baseline Demographics and Clinical Characteristics

	Gemcitabine for Injection/Carboplatin	Carboplatin
Number of randomized patients	178	178
Median age, years	59	58
Range	36 to 78	21 to 81
Baseline ECOG performance status 0-1 ^a	94%	95%
Disease Status		
Evaluable	7.9%	2.8%
Bidimensionally measurable	91.6%	95.5%
Platinum-free interval ^b		
6-12 months	39.9%	39.9%
>12 months	59.0%	59.6%
First-line therapy		
Platinum-taxane combination	70.2%	71.3%
Platinum-non-taxane combination	28.7%	27.5%
Platinum monotherapy	1.1%	1.1%

^a Nine patients (5 on the Gemcitabine for Injection plus carboplatin arm and 4 on the carboplatin arm) did not have baseline Eastern Cooperative Oncology Group (ECOG) performance status recorded.

^b Three patients (2 on the Gemcitabine for Injection plus carboplatin arm and 1 on the carboplatin arm) had a platinum-free interval of less than 6 months.

Table 11: Gemcitabine for Injection Plus Carboplatin Versus Carboplatin in Ovarian Cancer - Results of Efficacy Analysis

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

^a Treatment adjusted for performance status, tumor area, and platinum-free interval.

^b Partial response non-measurable disease

^c Independent reviewers could not evaluate disease demonstrated by sonography or physical exam.

^d Log Rank, unadjusted

^e Chi Square

^f Independently reviewed cohort - Gemcitabine for Injection /Carboplatin N=121, Carboplatin N=101

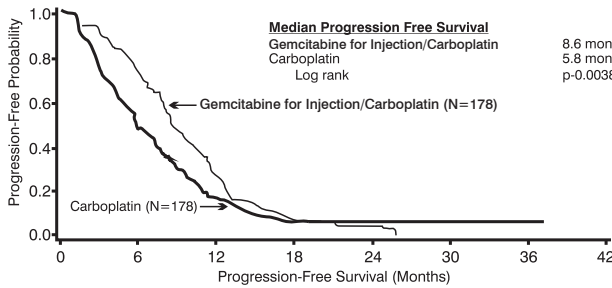


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemcitabine for Injection Plus Carboplatin Versus Carboplatin in Ovarian Cancer (N=356)

14.2 Breast Cancer

Data from a multi-national, randomized Phase 3 study (529 patients) support the use of Gemcitabine for Injection in combination with paclitaxel for treatment of breast cancer patients who have received prior adjuvant/neoadjuvant anthracycline chemotherapy unless clinically contraindicated. Gemcitabine for Injection 1250 mg/m² was administered on Days 1 and 8 of a 21-day cycle with paclitaxel 175 mg/m² administered prior to Gemcitabine for Injection on Day 1 of each cycle. Single-agent paclitaxel 175 mg/m² was administered on Day 1 of each 21-day cycle as the control arm.

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 monotherapy with paclitaxel as shown in Table 12 and Figure 2. Final survival analysis results at 440 events were Hazard Ratio of 0.86 (95% CI 0.71 – 1.04) for the ITT population, as shown in Table 12.

Table 12: Gemcitabine for Injection Plus Paclitaxel Versus Paclitaxel in Breast Cancer

	Gemcitabine for Injection /Paclitaxel	Paclitaxel
Number of patients	267	262
Median age, years	53	52
Range	26 to 83	26 to 75
Metastatic disease	97.0%	96.9%
Baseline KPS ^a ≥90	70.4%	74.4%
Number of tumor sites		
1-2	56.6%	58.8%
≥3	43.4%	41.2%
Visceral disease	73.4%	72.9%
Prior anthracycline	96.6%	95.8%
Overall Survival ^b		
Median (95% CI)	18.6 (16.5, 20.7)	15.8 (14.1, 17.3)
Hazard Ratio (95% CI)	0.86 (0.71, 1.04)	
Time to Documented Disease Progression ^c		
Median (95% C.I.), months	5.2 (4.2,5.6)	2.9 (2.6, 3.7)
Hazard Ratio (95% C.I.)	0.650 (0.524,0.805)	
Overall Response Rate ^d (95% C.I.)	40.8% (34.9, 46.7)	22.1% (17.1, 27.2)

^a Karnofsky Performance Status.

^b Based on the ITT population