HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Gemcitabine for Injection safely and effectively. See ful ormation for Gemcitabine for Injection

Gemcitabine for Injection, Powder, Lyophilized, For Solution For Intravenous Use

-----INDICATIONS AND USAGE-

- Ovarian cancer in combination with carbophain (1. Breast cancer in combination with paclitaxel (1.2) Non-small cell lung cancer in combination with cis Pancreatic cancer as a single-agent (1.4)

Gemcitabine for Injection is a nucleoside metabolic inhibitor indicated for

- 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)
- scriedure, 1200 mg/m² over 30 minutes on Days 1 and 8 or 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)
- --DOSAGE FORMS AND STRENGTHS-200 mg vial for injection (3)
- 1 g vial for injection (3) 2 g vial for injection (3)

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 nepatic 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)

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

See 17 for PATIENT COUNSELING INFORMATION

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17.1 Low Blood Cell Counts 17.3 Nursing Mothers

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

abine 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

abine for 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

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

1.4 Pancreatic Vancer
Gemclatibine 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.

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

Gemcitabine for Injection should be administered intravenously at a dose of 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21day 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 pranulocyte count > 1500 x 106/L and a platelet count > 100,000 x 106/L prior to each cycle.

Contravious demonstration for Injection dosage adjustments for hematological toxicity within a cycle of treatment is based on the granulocyte and gemeritabline for Injection dosage should be modified demonstration. If marrow suppression is detected, Gemeritabline for Injection dosage should be modified Gemeritabline for Injection is co according to guidelines in Table 1.

| Absolute granulocyte count (x 10 ⁶ /L) | | Platelet count (x 10 ⁶ /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 5.2 Hematolog held or decreased by 50% depending on the judgment of the treating physician. For carboplatin dosage adjustment, see manufacturer's

Dose adjustment for Gemcitabine for Injection in combination with carboplatin for subsequent cycles is based upon observed toxicity.

- te dose of Gericiabine for injection in subsequent cycles snot llowing hematologic toxicities: Absolute granulocyte count <500 x 10⁶/L for more than 5 days
- Absolute granulocyte count <100 x 106/L for more than 3 days Febrile neutro
- Platelets <25,000 x 10⁶/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

2.2 Breast Cancer

Gemotiabine 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 Gemotiabine 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 106/L and a platelet count ≥ 100.000 x 106/L prior to each cycle.

Dose Modifications

one for Injection dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on Day 8 of

| | 17 | , | , | 3 | 5 5 | |
|---|------------------------|-----------------------|-----------------|---------------------------------------|---------------------|--|
| | Table 2: Day | 8 Dosage Reduction Gu | idelines for Ge | emcitabine for Injection in Combina | ion with Paclitaxel | |
| Ξ | Absolute granulocyte c | ount (x 106/L) | | Platelet count (x 10 ⁶ /L) | % of full dose | |
| Ξ | ≥1200 | | and | >75,000 | 100 | |
| | 1000-119 | 9 | 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 Isee Clinical Studies (14.3)1. With the 4-week two scriedules have been investigated and the optimum schedule has not been determined [see Clinical Studies (14.5)]. With the 4-week schedule, Gemicitabine 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

page adjustments for hematologic toxicity may be required for Gemcitabine for Injection and for cisplatin. Gemcitabine for Injection dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients uosage adjustinent in Heritatorigica toxicity is assessed in the grainfunctive and platent counts taken in the ag of delapty. Padents 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

oine for Injection should be administered by intravenous infusion at a dose of 1000 mg/m² over 30 minutes once weekly for up to definition in the control should be administered by interviews intuition at a cose of root fright over 30 minutes once weekly for 37 weeks (or uniform the attenuant to the weekly for 3 consecutive weeks out of every 4 weeks.

<u>Dose Modifications</u>
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 drugs. dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be nodified or suspended according to the guidelines in Table 3.

| | Table 3: Dosage Red | duction Guidelines | |
|---|---------------------|---------------------------------------|----------------|
| Absolute granulocyte count (x 10 ⁶ /L) | | Platelet count (x 10 ⁶ /L) | % of full dose |
| ≥1000 | and | ≥100,000 | 100 |
| 500-999 | or | 50,000-99,999 | 75 |
| -500 | | -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 sub increased by 25%, provided that the absolute granulocyte count (AGC) and platelet nadirs exceed 1500 x 106/L, and 100,000 x 106/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 10%L and 100,000 x 10%L, respectively, and that non-hematologic toxicity has not been greater than

Caution should be exercised in handling and preparing Gemcitabine for Injection solutions. The use of gloves is recomm 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, hypoactivity, 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 gemoit ntration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg india 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 because it is consistent on the constitution will be 5.26 mL or 26.3 mL or 52.6 mL as 0.1 mg/mL.

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 natter and discoloration prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do

When prepared as directed. Gemcitabine for Injection solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° when prepared as directed, derictabilitie to injection solutions are stable to 24 hours at continued both temperature 20 to 20 C (to 77°F) [see USP Controlled Room Temperature]. Discard unused portion. Solutions of reconstituted Gemcitabine for Injection sho 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 DOSAGE FORMS AND STRENGTHS

citabine 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.

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

WARNINGS AND PRECAUTIONS therapy with Gemcitabine for Injection should be monitored closely by a physician experienced in the use of cancer

chemotherapeutic agents

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)]

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)]

r Gemcitabline for Injection in combination with carboplatin for subsequent cycles is based upon observed construction.

tabine for Injection in subsequent cycles should be reduced to 800 mg/m² on Days 1 and 8 in case of any of the Pulmonary toxicity has been reported with the use of Gemcitabine for Injection. In cases of severe lung toxicity, Gemcitabine for Injection and toxicity has been reported with the use of Gemcitabine for Injection. In cases of severe lung toxicity, Gemcitabine for Injection and toxicity has been reported with the use of Gemcitabine for Injection. therapy should be discontinued immediately and appropriate supportive care measures instituted [see Adverse Reactions (6.1 and 6.2)].

molytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine for Injection

Gemcitabine for Injection should be used with caution in patients with preexisting renal impairment as there is insufficient information Renal - In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic from clinical studies to allow clear dose recommendation for these patient populations. [see Use In Specific Populations (8.6)]

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)].

exacerbation of the underlying hepatic insufficiency. Isee Use In Specific Populations (8.7)

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 infor 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

5.6 Pregnancy
Gemcitabline for Injection can cause fetal harm when administered to a pregnant woman. In pre-clinical studies in mice and rabbits, genicitatine was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of Gemicitabine 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)]

Patients receiving Germicitabine for Injection should be monitored prior to each dose with a complete blood count (CBC), including Edema - Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected. (see due to edema. Dosage and Administration (2.1, 2.2, 2.3, and 2.4)1

Laboratorv evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter [see

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)- Preclinical and clinical studies have shown that Gemcitabine for Injection has Concurrent (given together or
 / days apart)
 Preclinical and clinical studies have shown that Gemicitabine for Injection has radiosensitizing activity. Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of Gemicitabine for Injection, frequency of Gemicitabine for Injection administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. In a single trial, where Gemicitabine 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

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug In the Gemcitabine for Injection plus cisplatin versus etoposide plus cisplatin study, dose adjustments occurred with 20% of Ger 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.

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 Gemcitabing patients with particular cancer. Adverse reactions reported in the single-agent safety database resident in discontinuation of definitioning 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

nal, Pulmonary and Infection categories. Table 4: Selected WHO-Graded Adverse Reactions in Patients Receiving Single-Agent Gemcitabine for Injection WHO Grades (% incidence)^a

| | A | II Patients ^b | | Pancrea | itic Cancer | Discontinuations (%)d | |
|-----------------------------|------------|--------------------------|---------|------------|-------------|-----------------------|--------------|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 | All Patients |
| Laboratorye | | | | | | | |
| 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 | | | | | | | <1 |
| ALT | 68 | 8 | 2 | 72 | 10 | 1 | |
| AST | 67 | 6 | 2 | 78 | 12 | 5 | |
| Alkaline Phosphatase | 55 | 7 | 2 | 77 | 16 | 4 | |
| Bilirubin | 13 | 2 | <1 | 26 | 6 | 2 | |
| Renal | | | | | | | <1 |
| Proteinuria | 45 | <1 | 0 | 32 | <1 | 0 | |
| Hematuria | 35 | <1 | 0 | 23 | 0 | 0 | |
| BUN | 16 | 0 | 0 | 15 | 0 | 0 | |
| Creatinine | 8 | <1 | 0 | 6 | 0 | 0 | |
| Non-laboratory ^f | | | | | | | |
| 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 |

| Grade based on criteria from the World Health Organization (WHO). |
|---|
| N=699-974; all patients with laboratory or non-laboratory data. |
| N=161-241; all pancreatic cancer patients with laboratory or non-laboratory data. |

d N=979.

ratory data with incidence for all patients ≥ 10%. For approximately 60% of the patients, non-laboratory adverse reactions were graded only if assessed to be possibly drug-related. Hematologic - In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemcitabine for Injection, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of

patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelo for Injection therapy and dosage modified or suspended according to the degree of hematologic toxicity. *Isee Dosage and Administration* (2.1, 2.2, 2.3, and 2.4))

Gastrointestinal - Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and

Hepatic - In clinical trials, Gemcitabine for Injection was associated with transient elevations of one or both serum transaminases in Hepatic - In clinical trials, Gemicitatione for Injection was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemicitation for Injection or with greater total cumulative dose. 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. [see Adverse Reactions (6.2)1

National Initial Initials, mile price in the Periody of Charles and the Periody of Charles Initials Considered in the Periody of Charles Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gencitabine for Injection in clinical trials. Four patients developed HUS on Gemcitabine for Injection therapy, 2 immediately posttherapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine for Injection therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required. [see Adverse Reactions (6.2)]

Fever - The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemcitabine for Injection may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash - Rash was renorted in 30% of natients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild

Pulmonary - In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemcitabine for Injection therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Germcitabine for Injection. [see Adverse Reactions (6.2)] The etiology of these effects is unknown. If such effects develop, Germcitabine for Injection should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Flu-like Symptoms - "Flu syndrome" was reported for 19% of patients, Individual symptoms of fever, asthenia, anorexia, headache.

cough, child, and myalgia were commonly reported. Fever and asthenia were also reported frequently. As isolated symptoms. Insomnia, thinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection - Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia - Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity- There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation - Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemcitabine for Injection is not a vesicant. Allergic - Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemcitabine for

Injection should not be administered to patients with a known hypersensitivity to this drug [see Contraindications (4)] such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior historicardiovascular disease [see Adverse Reactions (6.2)]. Cardiovascular - During clinical trials, 2% of patients discontinued therapy with Gemcitabine for Injection due to cardiovascular even

Combination Use in Non-Small Cell Lung Cancer:

In the Gemcitabine for Injection plus cisplatin versus cisplatin study, dose adjustments occurred with 35% of Gemcitabine for Injections receiving large volumes of radiotherapy [median treatment volumes 4795 cm³]. Subsequent studies have been reported and suggest that Gemicitabine for Injection administrated at lower doses with concurrent radiotherapy has predictable and less severe toxicity. However, the optimum regimen for safe administration of Gemicitabine for Injection administration of Gemicitabine for Injection administration of Gemicitabine for Injection with therapeutic doses of radiation has not yet been determined in page 11 of 20 pages of the community of the page 12 pages 12 pages

> for Injections and 16% of cisplatin injections in the Gemcitabine for Injection plus cisplatin arm compared with 20% of etoposide injections and 15% of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of Gemcitabine for Injection plus injections and 15% of esplant injections in the eloposize pink esplant and v. With a fluctual of 5 cycles of elementations of injection plus cisplatin treatment, 15 of 69 patients (22%) experienced 15 hospitalizations due to possibly treatment-related adverse reactions. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27%) experienced 22 hospitalizations due to possibly treatment-related adverse reactions. In patients who completed more than one cycle, dose adjustments were reported in 81% of the demotabline for Injection plus cisplatin patients, compared with 68% on the etoposide plus cisplatin arm. Study discontinuations for possibly drug-related adverse reactions occurred in 14% of patients on the Gemcitabine for Injection plus cisplatin arm and in 8% of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemcitabine for Injection plus cisplatin treatment (\sim 90%) compared to that with the Gemcitabine for Injection monotherapy (\sim 60%). With combination therapy Gemcitabine for Injection dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments

Table 5 presents the safety data from the Gericitabine for Injection plus cisplatin versus cisplatin study in non-small cell lung cancer. The NCI Common Toxicity Criteria (CTC) were used. 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. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm. More patients required RBC and platelet transfusions on the Gemcitabine for Injection plus cisplatin arm.

Myelosuppression occurred more frequently on the combination arm, and in 4 possibly treatment-related deaths myelo wyerosuppression occurred more trequently on the combination arm, and in 4 possibly treatment-related deaths myerosuppression was observed. Sepsis was reported in 4% of patients on the Gemcitabine for Injection plus cisplatin arm compared to 1% on the cisplatin arm. Platelet transfusions were required in 21% of patients on the combination arm and <1% of patients on the cisplatin arm. Hemorrhagic events occurred in 14% of patients on the combination arm and 4% on the cisplatin arm. However, severe hemorrhagic events were required in 39% of the patients on the Gemcitabine for Injection plus cisplatin arm, versus 13% on the cisplatin arm. The data suggest cumulative anemia with continued Gemcitabine for Injection plus cisplatin use.

was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical, and neurocerebellar toxicity occurred more often with Gemcitabine for Injection plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms. Cardiac dysrrhythmias of Grade 3 or greater were reported in 7 (3%) patients treated with Gemcitabine for Injection plus cisplatin Cardiac dysrinyunnas or Glade 3 or greater were reported in 7 (3%) patients treated with certicitatine for injection put compared to one (<1%) Grade 3 dysrriythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associone Grade 4 arrhythmia on the Gemcitabine for Injection plus cisplatin combination arm.

Nausea and vomiting despite the use of antiemetics occurred more often with Gemcitabine for Injection plus cisplatin therapy (78%) than

with cisplatin alone (71%). In studies with single-agent Gemcitabine for Injection, a lower incidence of nausea and vomiting (58% to 69%)

Table 6 presents data from the randomized study of Gemcitabine for Injection plus cisplatin versus etoposide plus cisplatin in 135 patients with NSCLC. One death (1.5%) was reported on the Gemcitabine for Injection plus cisplatin arm due to febrile neutropenia associated with renal failure which was possibly treatment-related. No deaths related to treatment occurred on the etoposide plus cisplatin arm. The overall incidence of Grade 4 neutropenia on the Gemcitabine for Injection plus cisplatin arm was less than on the cisplatin arm. Ine overall incidence of Grade 4 neutropenia on the Gericitabine for Injection plus cisplatin arm (28% versus 56%). Sepsis was experienced by 2% of patients on both treatment arms. Grade 3 anemia and Grade 3/4 thrombocytopenia were more common on the Gericitabine for Injection plus cisplatin mrn. RBC transfusions were given to 29% of the patients who received Gericitabine for Injection plus cisplatin versus 21% of patients who received etoposide plus cisplatin. Platelet transfusions were given to 3% of the patients who received Gericitabine for Injection plus cisplatin versus 8% of patients who received etoposide plus cisplatin. Grade 3/4 nausea and vomiting were also more common on the Gericitabine for Injection plus cisplatin. arm. On the Gemcitabine for Injection plus cisplatin arm, 7% of participants were hospitalized due to febrile neutropenia compared to 12% on the etoposide plus cisplatin arm. More than twice as many patients had dose reductions or omissions of a scheduled dose of Gemcitabine for Injection as compared to etoposide, which may explain the differences in the inclidence of neutropenia and febrile neutropenia between treatment arms. Flu syndrome was reported by 3% of patients on the Gemcitabine for Injection plus cisplatin arm with none reported on the comparator arm. Eight patients (12%) on the Gemcitabine for Injection plus cisplatin arm reported edema compared to one patient (2%) on the etoposide plus cisplatin arm.

Table 5: Selected CTC-Graded Adverse Reactions From Comparative Trial of Gemcitabine for Injection Plus Cisplatin Versus Single-Agent Cisplatin in NSCLC CTC Grades (% incidence)^a Gemcitabling for Injection, plus Cisplatin ^b

| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
|------------------------------------|------------|---------|---------|------------|---------|---------|
| _aboratory ^d | | | | | | |
| -lematologic | | | | | | |
| Anemia | 89 | 22 | 3 | 67 | 6 | 1 |
| RBC Transfusion ^e | 39 | | | 13 | | |
| Leukopenia | 82 | 35 | 11 | 25 | 2 | 1 |
| Neutropenia | 79 | 22 | 35 | 20 | 3 | 1 |
| Thrombocytopenia | 85 | 25 | 25 | 13 | 3 | 1 |
| Platelet Transfusions ^e | 21 | | | <1 | | |
| Lymphocytes | 75 | 25 | 18 | 51 | 12 | 5 |
| lepatic | | | | | | |
| Transaminase | 22 | 2 | 1 | 10 | 1 | 0 |
| Alkaline Phosphatase | 19 | 1 | 0 | 13 | 0 | 0 |

lyperglycemia Diarrhea Neuro Sensory Infection Neuro Cortical Neuro Mood

N=217-253, all Genditabline for Injection plus cisplatin patients with laboratory or non-laboratory data. Genditabline 1000 mg/m² on Days 1, 8, and 15 and cisplatin at 100 mg/m² on Day 1 every 28 days.

N=213-248; all cisplatin patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 every 28 days.

Percent of patients receiving transfusions. Percent transfusions are not CTC-graded events

Non-laboratory events were graded only if assessed to be possibly drug-relate

Table 6: Selected WHO-Graded Adverse Reactions From Comparative Trial of Gemcitabine for Injection Plus Cisplatin Versus Etoposide Plus Cisplatin in NSCLC

| | Gemcitabine for In | | Cisplatin ^b | Etoposide plus Cisplatin ^c | | |
|------------------------------------|--------------------|---------|------------------------|---------------------------------------|---------|---------|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Laboratory ^d | | | | | | |
| Hematologic | | | | | | |
| Anemia | 88 | 22 | 0 | 77 | 13 | 2 |
| RBC Transfusions ^e | 29 | | | 21 | | |
| Leukopenia | 86 | 26 | 3 | 87 | 36 | 7 |
| Neutropenia | 88 | 36 | 28 | 87 | 20 | 56 |
| Thrombocytopenia | 81 | 39 | 16 | 45 | 8 | 5 |
| Platelet Transfusions ^e | 3 | | | 8 | | |
| Hepatic | | | | | | |
| ALT | 6 | 0 | 0 | 12 | 0 | 0 |
| AST | 3 | 0 | 0 | 11 | 0 | 0 |
| Alkaline Phosphatase | 16 | 0 | 0 | 11 | 0 | 0 |
| Bilirubin | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal | | | | | | |
| Proteinuria | 12 | 0 | 0 | 5 | 0 | 0 |
| Hematuria | 22 | 0 | 0 | 10 | 0 | 0 |
| BUN | 6 | 0 | 0 | 4 | 0 | 0 |
| Creatinine | 2 | 0 | 0 | 2 | 0 | 0 |
| Non-laboratory ^{f, g} | | | | | | |
| Nausea and Vomiting | 96 | 35 | 4 | 86 | 19 | 7 |
| Fever | 6 | 0 | 0 | 3 | 0 | 0 |
| Rash | 10 | 0 | 0 | 3 | 0 | 0 |
| Dyspnea | 1 | 0 | 1 | 3 | 0 | 0 |
| Diarrhea | 14 | 1 | 1 | 13 | 0 | 2 |
| Hemorrhage | 9 | 0 | 3 | 3 | 0 | 2 |
| Infection | 28 | 3 | 1 | 21 | 8 | 0 |
| Alopecia | 77 | 13 | 0 | 92 | 51 | 0 |
| Stomatitis | 20 | 4 | 0 | 18 | 2 | 0 |
| Somnolence | 3 | 0 | 0 | 3 | 2 | 0 |
| Paresthesias | 38 | 0 | 0 | 16 | 2 | 0 |

N=67-69; all Gemcitabine for Injection plus cisplatin patients with laboratory or non-laboratory data. Gemcitabine for Injection at 1250

mg/m² on Days 1 and 8 and cisplatin at 100 mg/m² on Day 1 every 21 days. N=57-63; all cisplatin plus etoposide patients with laboratory or non-laboratory data. Cisplatin at 100 mg/m² on Day 1 and intravenous etoposide at 100 mg/m² on Days 1, 2, and 3 every 21 days.

Regardless of causality.

Percent of patients receiving transfusions. Percent transfusions are not WHO-graded events. normal or patients receiving transfusions. Percent transfusions are not WHO Non-laboratory events were graded only if assessed to be possibly drug-relative Pain data were not collected.

Combination Use in Breast Cancer:
In the Gemcitabine for Injection plus paclitaxel versus paclitaxel study, dose reductions occurred with 8% of Gemcitabine for Injections and 5% of paclitaxel injections on the combination arm, versus 2% on the paclitaxel arm. On the combination arm, 7% of Gemcitabine for Injection doses were omitted, compared to <1% of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7%) on the Gemcitabine for Injection plus paclitaxel arm and 12 (5%) on the paclitaxel arm discontinued the study

because of adverse reactions. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug-related, one on each arm. Table 7 presents the safety data occurrences of ≥10% (all grades) from the Gemcitabine for Injection plus paclitaxel versus paclitaxe

Table 7: Adverse Reactions From Comparative Trial of Gemcitabine for Injection Plus Paclitaxel Versus Single-Agent Paclitaxel in Breast Can

CTC Grades (% incidence)

| | Gemcitabine for Injection plu | s Paclitaxel (| Gemcitabine for Injection plus Paclitaxel (N=262) | | | 59) |
|-----------------------------|-------------------------------|----------------|---|------------|---------|---------|
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Laboratory ^b | | | | | | |
| Hematologic | | | | | | |
| Anemia | 69 | 6 | 1 | 51 | 3 | <1 |
| Neutropenia | 69 | 31 | 17 | 31 | 4 | 7 |
| Thrombocytopenia | 26 | 5 | <1 | 7 | <1 | <1 |
| Leukopenia | 21 | 10 | 1 | 12 | 2 | 0 |
| Hepatobiliary | | | | | | |
| ALT | 18 | 5 | <1 | 6 | <1 | 0 |
| AST | 16 | 2 | 0 | 5 | <1 | 0 |
| Non-laboratory ^c | | | | | | |
| Alopecia | 90 | 14 | 4 | 92 | 19 | 3 |
| Neuropathy-sensory | 64 | 5 | <1 | 58 | 3 | 0 |
| Nausea | 50 | 1 | 0 | 31 | 2 | 0 |
| Fatigue | 40 | 6 | <1 | 28 | 1 | <1 |
| Myalgia | 33 | 4 | 0 | 33 | 3 | <1 |
| Vomiting | 29 | 2 3 | 0 | 15 | 2 2 | 0 |
| Arthralgia | 24 | 3 | 0 | 22 | 2 | <1 |
| 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 |

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

Non-laboratory events were graded only if assessed to be possibly drug-related

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Front Side

The following are the clinically relevant adverse reactions that occurred in >1% and <10% (all grades) of patients on either arm. In 8.6 Renal parentheses are the incidences of Grade 3 and 4 adverse reactions (Gemcitabline for Injection plus paclifaxe) versus paclifaxe); febrile Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabline for Injection

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

Combination Use in Ovarian Cance

patients younger than 65.

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 ses on the carboplatin alone arm. There were no differences in discontinuations due to adverse reactions between arms (10.9% versus

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 Cancera

| CTC Grades (% incidence) | | | | | | |
|------------------------------------|---------------------------|----------------|------------|---------------------|---------|---------|
| | Gemcitabine for Injection | olus Carboplat | in (N=175) | Carboplatin (N=174) | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| Laboratory ^b | | | | | | |
| Hematologic | | | | | | |
| Neutropenia | 90 | 42 | 29 | 58 | 11 | 1 |
| Anemia | 86 | 22 | 6 | 75 | 9 | 2 |
| 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 |
| 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 |
| 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 |

Grade based on Common Toxicity Criteria (CTC) Version 2.0 (all grades ≥10%). Regardless of causality.

Percent of patients receiving transfusions. Transfusions are not CTC-graded events. Blood transfusions included both packed red

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

agents were administered more frequently with combination therapy than with monotherapy (granulocyte growth factors: 23.6% and or 2 g of gemcitabine HCI (expressed as free base) formulated with mannitol (200 mg, 1 g or 2 g respectively) and sodium acetate (12.5%). 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 involving are the clinically relevant adverse relactions, regardness of castassing, lital occurred in 2 18 and 4 color and grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse reactions (Germictabine for Injection plus carboplatin to versus carboplatin): AST or ALT elevation (0 versus 1.2%), dyspnea (3.4% versus 2.9%), febrile neutropenia (1.1% versus 0), 12.1 Mechanism of Action hemorrhagic event (2.3% versus 1.1%), hypersensitivity reaction (2.3% versus 2.9%), motor neuropathy (1.1% versus 0.6%), and

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

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 Gemoitabine for Injection

Cardiovascular - Connective 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,

Centifies and information information including degradations in the absence of extravasation have been rately reported. Severe skill reactions, including degradation 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

inter tailute and usern reported very ratery in patents receiving certification for injection affice of injection affice. Hepatic veno-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

various manifications. Some patients experience the offset of particular symptoms by 0.2 weeks after the last deficulation of linjection 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. y, 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, Isee Clinical Pharmacology (12.2 and 12.3)]

8 USE IN SPECIFIC POPULATIONS

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

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

til 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.

The discontinue for Injection in the drug to the mother infusion (<70 min).

Gemcitabine half-life for short infusions ranged from 42 to

8.4 Pediatric Use

The safety and effectiveness of Gemcitabine for Injection in pediatric natients has not been established. Gemcitabine for Injection was rile sately and enterouveness of entroutions of injection in pecuative patients has not been established, entroutination to 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.

Gemcitabline for Injection clearance is affected by age Isee Clinical Pharmacology (12.3)1. There is no evidence, however, that unusual desinctabilité oil injection l'écalitation et a insecteur y age (see crimina i namacony) (12.01). There is no evolution, indée in des 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 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 induced forward mutations in vitro in a mouse lymphoma (L5178Y) assay and was clastogenic in an in vivo mouse micronucleus assay. under the composition 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 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 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

remarks are the incustries of clause 3 and 4 adverse reactions (definition in injection plus pacinazer) results (0.9% versus 1.2%), infection (0.8% versus 0.8%), dyspnea (1.9% versus 0), and allergic reaction/hypersensitivity (0 versus 6).

Remarks of the injection (0.8% versus 0.8%), dyspnea (1.9% versus 0.9%), and allergic reaction/hypersensitivity (0 versus 6).

Remarks of the injection (0.8% versus 0.8%), dyspnea (1.9% versus 0.9%), and allergic reaction/hypersensitivity (0 versus 6).

Remarks of the injection (0.8% versus 0.8%), dyspnea (1.9% versus 0.9%), and allergic reaction/hypersensitivity (0 versus 6).

Gemcitabline 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)]

Serious hepatotoxicity, including liver failure and death, has been reported in patients receiving Gerncitabine 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)]

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.

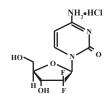
10 OVERDOSAGE

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 principal toxicutes seen when a single cuse as high as 5700 might was administered by lindarenous industrial over 50 minutes even weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate to 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'-

The structural formula is as follows:



The empirical formula for gemcitabine HCI is C₉H₁₁F₂N₃O₄ • HCI. It has a molecular weight of 299.66.

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 g, 62.5 mg or 125 mg respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been adde

12 CLINICAL PHARMACOLOG

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progressio of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate or cells through the G17s-phase boundary. Generationine is metabolized intracellulary by nucleoside kinases to the active diphosphate (dfGCDP) and triphosphate (dfGCDP) and triphosphate by 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 thin is enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, 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 concennation of outry toy are accord of the diphosphate) enhances the incorporation of genicitation entriposphate into DNA (self-potentiation). After the genicitation enucleotide 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 gemicitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemicitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin in vitro. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, genicitabine 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

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

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/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 duratio of infusion and gender. Gemcitabine plasma protein binding is negligible.

metabulish (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.

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentration 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-I ife for the "Typical" Patien

| Age | e Cle | arance Men (L/hr/m²) | Clearance Women (L/hr/m2) | Half-Life ^a Men (min) | Half-Lifea 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 |

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

Drug Interactions

when Gernciaonie for injection (1250 mg/m² on Lays 1 and 8) and cisplatin (15 mg/m² on Lay 1) were administered in NSULD patients, the clearance of gerncitable on Day 1 was 128 L/h/m² and on Day 8 was 107 L/h/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

mg/m² basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased inglant basis in I make linke had an elect on letting with moderate to severe hypospermatogeness, decleased remay, and decleased 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

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 singleagent carboplatin AUC 5 administered on Day 1 of each 21-day cycle as the control arm. The primary endpoint of this study was ession free survival (PFS).

Patient characteristics are shown in Table 10. The addition of Gemcitabine for Injection to carboplatin resulted in statistically significan 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 mcitabine 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

| | 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% |

- Cooperative Oncology Group (ECOG) performance status recorded.
- Three patients (2 on the Gemcitabine for Injection plus carboplatin arm and 1 on the carboplatin arm) had a platinum-free interval of

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

| | Gerncitabline for injection / Carbopiatin ($N = 1/8$) | Carbopiatin (N=178) | | | | |
|--|---|---------------------|-----------------------|--|--|--|
| PFS Median (95%, C.I.) months | 8.6 (8.0,9.7) | 5.8 (5.2,7.1) | p=0.0038 ^d | | | |
| Hazard Ratio (95%, C.I.) | 0.72 (0.57, 0.90) | | | | | |
| Overall Survival Median (95%, C.I.) months | 18.0 (16.2, 20.3) | 17.3 (15.2, 19.3) | p=0.8977 ^d | | | |
| azard Ratio (95%, C.I.) 0.98 (0.78, 1.24) | | | | | | |
| Adjusted ^a Hazard Ratio (95%, C.I.) | 0.86 (0.67, 1.10) | | | | | |
| Investigator Reviewed | | | | | | |
| Overall Response Rate | 47.2% | 30.9% | p=0.0016e | | | |
| CR | 14.6% | 6.2% | | | | |
| PR+PRNM ^b | 32.6% | 24.7% | | | | |
| Independently Reviewed | | | | | | |
| Overall Response Rate ^{c,f} | 46.3% | 35.6% | p=0.11e | | | |
| CR | 9.1% | 4.0% | | | | |
| PR+PRNM | 37.2% | 31.7% | | | | |

- eatment adjusted for performance status, tumor area, and platinum-free interval Partial response non-measurable disease
- ndent reviewers could not evaluate disease demonstrated by sonography or physical exam
- Log Rank, unadjusted Chi Square
 - ohort Gemcitabine for Injection /Carbonlatin N=121, Carbonlatin N=101

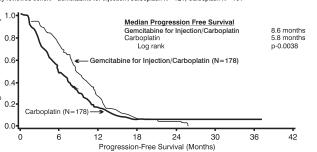


Figure 1: Kaplan-Meier Curve of Progression Free Survival in Gemcitabine for Injection Plus Carboplatin Versi Ovarian Cancer (N=356)

Data from a multi-national randomized Phase 3 study (529 natients) support the use of Gemcitabine for Injection in combination with Data from a finite-inational, automotized triales 5 study (229 patients) support to the use of definitional from international for injection in Commission Papacitizate for treatment of breast cancer patients who have received prior adjuvant/neoadjuvant arcycline chemotherapy unless clinically contraindicated. Gemotiabine 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.

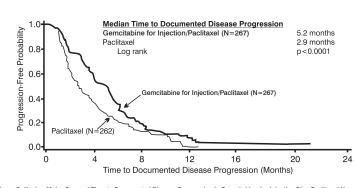
The addition of Gemcitabine for Injection to paclitaxel resulted in statistically significant improvement in time to documented disease progression and overall response rate compared to monotherapy with pacifixer as shown in Table 12 and Figure 2. Final survival analysis results at 440 events were Hazard Ratio of 0.86 (95%, Cl: 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 | | The first trial compared Gemcitabine for Injection to 5-Fluorouracil (5-FU) in patients who had received no prior chen |
|------------------------------------|---------------------------------------|--------------------|----------|---|
| Number of patients | 267 | 262 | | trial studied the use of Gemcitabine for Injection in pancreatic cancer patients previously treated with 5-FU or a 5-FU |
| Median age, years | 53 | 52 | | In both studies, the first cycle of Gemcitabine for Injection was administered intravenously at a dose of 1000 mg |
| Range | 26 to 83 | 26 to 75 | | once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatments |
| Metastatic disease | 97.0% | 96.9% | | for Injection. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks |
| Baseline KPS ^a ≥90 | 70.4% | 74.4% | | The primary efficacy parameter in these studies was "clinical benefit response," which is a measure of clinical im |
| Number of tumor sites | | | | analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in t |
| 1-2 | 56.6% | 58.8% | | formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either |
| ≥3 | 43.4% | 41.2% | | |
| Visceral disease | 73.4% | 72.9% | | i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consump |
| Prior anthracycline | 96.6% | 95.8% | | greater improvement in performance status (Karnofsky Performance Status) for a period of at least 4 consecu |
| Overall Survival ^b | | | | showing any sustained worsening in any of the other parameters. Sustained worsening was defined as 4 con |
| Median (95 %, CI) | 18.6 (16.5, 20.7) | 15.8 (14.1, 17.3) | | either any increase in pain intensity or analgesic consumption or a 20-point decrease in performance status occ |
| Hazard Ratio (95%, CI) | 0.86 (0.71, 1.04) | | | 12 weeks of therapy. OR: |
| Time to Documented Disease | | | p<0.0001 | ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight (|
| Progression ^c | | | | maintained for ≥ 4 weeks) not due to fluid accumulation. |
| Median (95%, C.I.), months | 5.2 (4.2,5.6) | 2.9 (2.6, 3.7) | | ' |
| Hazard Ratio (95%, C.I.) | 0.650 (0.524,0.80) | 5) | p<0.0001 | The first study was a multicenter (17 sites in US and Canada), prospective, single-blinded, two-arm, random |
| Overall Response Rate ^b | | | p<0.0001 | Gemcitabine for Injection and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had receive |
| (95%, C.I.) | 40.8% (34.9, 46.7) | 22.1% (17.1, 27.2) | | with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m² for 30 minutes. The |
| | | | | randomized trial are shown in Table 14. Patients treated with Gemeitabine for Injection had statistically significant |

Based on the ITT population

. ion of investigator and Independent Review Committee assessments according to a predefined algorithr



Paclitaxel Breast Cancer Study (N=529)

14.3 Non-Small Cell Lung Cancer (NSCLC)

a from 2 randomized clinical studies (657 patients) support the use of Gemcitabine for Injection in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine for Injection plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and Canada in 522 patients with

inoperable Stage IIIA, IIIB, or IV NSCIC who had not received prior chemotherapy. Gemiclabilities in 1922 parameters and inoperable stage IIIA, IIIB, or IV NSCIC who had not received prior chemotherapy. Gemiclabilities for Injection 1000 mg/m² was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m² administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m² was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. Patient demographics are shown in Table 13. An imbalance with regard to histology was observed with 48% of patients on the cisplatin arm and 37% of patients on the Gemcitabine for Injection plus cisplatin arm having adenocarcinoma.

The Kaplan-Meier survival curve is shown in Figure 3. Median survival time on the Gemcitabine for Injection plus cisolatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Log rank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Genetitabine for Injection plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank p=0.009, two-sided). The objective response rate on the Gemcitabine for Injection plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed Gemcitabine for Injection plus cisplatin versus etoposide plus cisplatin: A second, multicenter, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemcitabine for Injection 1250 mg/m² on Days 1 and 8, and cisplatin 100 mg/m² on Day 1 of a 21-day cycle

to the intervenous etoposited 100 mg/m² on Days 1, 2, and 3 and cisplatin 100 mg/m² on Day 1 of a 21-day cycle (Table 13). There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two-sided). The median survival was 8.7 months for the Gemcitabine for Injection plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemcitabine for Injection plus cisplatin arm was 5.0 months compared to 4.1 months on the eleposide plus cisplatin arm 4.1 months on the compared to 4.1 months on the eleposide plus cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the Gemcitabine for Injection plus cisplatin arm was 33 months compared to 4.1 months on the eleposide plus cisplatin arm 4.1 months of 4.1 months on the eleposide plus cisplatin arm 4.1 months of 4.1 months on the eleposide plus cisplatin arm 4.1 months of compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided).

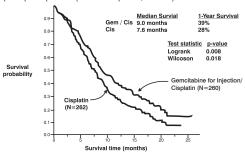


Figure 3: Kaplan-Meier Survival Curve in Gemcitabine for Injection Plus Cisplatin Versus Cisplatin NSCLC Study (N=522)

Table 13: Randomized Trials of Combination Therapy With Gemcitabine for Injection Plus Cisplatin in NSCLC

| mu | Lo uu | y concaute | _ | 21 day concusio | | |
|-------------------------|---|------------|------------|---|-------------------------|---------|
| Treatment Arm | Gemcitabine for Injection /Cisplatin | Cisplatin | | Gemcitabine for Injection /Cisplatin | Cisplatin/ Etoposide | |
| Number of patients | 260 | 262 | | 69 | 66 | |
| Male | 182 | 186 | | 64 | 61 | |
| Female | 78 | 76 | | 5 | 5 | |
| Median age, years | 62 | 63 | | 58 | 60 | |
| Range | 36 to 88 | 35 to 79 | | 33 to 76 | 35 to 75 | |
| Stage IIIA | 7% | 7% | | N/A ^c | N/Ac | |
| Stage IIIB | 26% | 23% | | 48% | 52% | |
| Stage IV | 67% | 70% | | 52% | 49% | |
| Baseline KPSd 70 to 80 | 41% | 44% | | 45% | 52% | |
| Baseline KPSd 90 to 100 | 57% | 55% | | 55% | 49% | |
| Survival | | | p=0.008 | | | p=0.18 |
| Median, months | 9.0 | 7.6 | i . | 8.7 | 7.0 | i . |
| (95%, C.I.) months | 8.2, 11.0 | 6.6, 8.8 | | 7.8, 10.1 | 6.0, 9.7 | |
| Time to Disease | | | | | | |
| Progression | | | p=0.009 | | | p=0.015 |
| Median, months | 5.2 | 3.7 | | 5.0 | 4.1 | |
| (95%, C.I.) months | 4.2, 5.7 | 3.0, 4.3 | | 4.2, 6.4 | 2.4, 4.5 | |
| Tumor Dooponoo | 260/ | 100/ | n <0.00018 | 220/ | 1.40/ | n_0.018 |

10% p<0.0001° 28-day schedule - Gemcitabine for Injection plus cisplatin: Gemcitabine for Injection 1000 mg/m² on Days 1, 8, and 100 mg/m² on Day 1 every 28 days; Single-agent cisplatin: cisplatin 100 mg/m² on Day 1 every 28 days.

21-day schedule - Gemcitabine for Injection plus cisplatin: Gemcitabine for Injection 1250 mg/m² on Days 1 and 8 and cisplatin 100 mg/m² on Day 1 every 21 days; Eloposide plus Cisplatin: cisplatin 100 mg/m² on Day 1 and intravenous etoposide 100 mg/m² on Days 1, 2, and 3 every 21 days.

N/A Not applicable. es were calculated using the Log rank test for difference in overall time to an event.

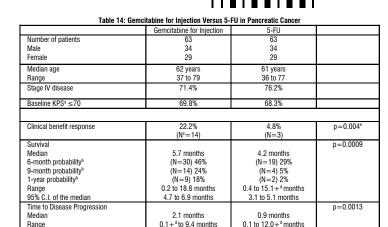
Karnofsky Performance Status

Data from 2 clinical trials evaluated the use of Gemcitabine for Injection in patients with locally advanced or metastatic pancreatic cancer. The first trial compared Generatable for Injection to 5-Fluorogracil (5-FU) in patients who had received no prior chemotherapy. A second The lins that compared certification for injection in parcreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of Gemcitabine for Injection was administered intravenously at a dose of 1000 mg/m² over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitated holding a dose) followed by a week of rest from treatment with Gemcitabine

The primary efficacy parameter in these studies was "clinical benefit response" which is a measure of clinical improvement based of analgesic consumption, pain intensity, performance status, and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the 2 trials. A patient was considered a clinical benefit responder if either:

- i) the patient showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Kamofsky 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
- ii) the patient was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase

The first study was a multicenter (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of Gemcitabine for Injection and 5-FU in patients with locally advanced or metastatic pancreatic cancer who had received no prior treatment with chemotherapy. 5-FU was administered intravenously at a weekly dose of 600 mg/m² for 30 minutes. The results from this randomized trial are shown in Table 14. Patients treated with Gemcitabine for Injection had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 4. No confirmed objective tumor responses were observed with either treatment



- No progression at last visit; remains alive.

 The p-value for clinical benefit response was calculated using the two-sided test for difference in binomial proportions. All other p-values were calculated using the Log rank test for difference in overall time to an event.

1.9 to 3.4 months

Clinical benefit response was achieved by 14 patients treated with Gerncitabine for Injection and 3 patients treated with 5-FU. One patient omnical penetri response was achieved by 14 patients treated with Gemcitabine for Injection and 3 patients treated with 5-FU. One patient on the Gemcitabine for Injection arm showed improvement in all 3 primary parameters (pain intensity, analgesic consumption, and performance status). Eleven patients on the Gemcitabine for Injection arm and 2 patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the Gemcitabine for Injection arm showed improvement in analgesic consumption or pain intensity with improvement in performance status. One patient on the 5-FU arm was stable with regard to pain intensity and analgesic consumption with improvement in performance status. No patient on either arm achieved a clinical benefit response based on weight gain.

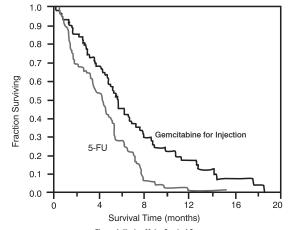


Figure 4: Kaplan-Meier Survival Curve

The second trial was a multicenter (17 US and Canadian centers), open-label study of Gerncitabine for Injection in 63 patients with advanced pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen. The study showed a clinical benefit response rate of 27% and median survival of 3.9 months.

14.5 Other Clinical Studies
When Gemcitabline for Injection was administered more frequently than once weekly or with infusions longer than 60 minutes, increased toxicity was observed. Results of a Phase 1 study of Gemcitabine for Injection to assess the maximum tolerated dose (MTD) on a daily x 5 schedule showed that patients developed significant hypotension and severe flu-like symptoms that were intolerable at doses above 10 mg/m². The incidence and severify of these events were dose-related. Other Phase 1 studies using a fuel-eweekly schedule reached MTDs of only 65 mg/m² (30-minute infusion) and 150 mg/m² (5-minute bolus). The dose-limiting toxicities were thrombocytopenia and flu-like symptoms, particularly asthenia. In a Phase 1 study to assess the maximum tolerated infusion time, clinically significant toxicity, defined as myelosuppression, was seen with weekly doses of 300 mg/m² at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion [see Clinical Pharmacology (12.3)] and the toxicity appears to be increased if Gemcitabine for Injection is administered more frequently than once weekly or with infusions longer than 60 minutes [see Warnings and Precautions (5.1)1

15. REFERENCES

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American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs: Am J Health-Syst Pharm. 2006;

Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society. HOW SUPPLIED/STORAGE AND HANDLING

Gemoitabine for Injection, USP is available in sterile single-use vials individually packaged in a carton containing:

200 mg white, Ivophilized powder in a sterile single use vial NDC 0069-3857-10 1 g white, Ivophilized powder in a sterile single use vial NDC 0069-3858-10

2 g white, lyophilized powder in a sterile single use vial NDC 0069-3859-10 p-value for tumor response was calculated using the two-sided Fisher's Exact test for difference in binomial proportions. All other p-

Jnopened vials of Gemcitabine for Injection are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F) [See USP Controlled Room Temperature]. [see Dosage and Administration (2.5 and 2.6)].

PATIENT COUNSELING INFORMATION 17 PATIENT COUNSELING I 17.1 Low Blood Cell Counts

Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately contact their physician should any sign of infection develop including fever. Patients should also contact their physician if bleeding or symptoms of anemia occur. Isea Warnings and Precautions (5.2)] 17.2 Pregnancy

There are no adequate and well-controlled studies of Gemcitabine for Injection in pregnant women. Based on animal studies Gemcitabine

for Injection can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the risks to the fetus need to be discussed with their physician. [see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)]

17.3 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. [see Use in Specific Populations (8.3)]

Pfizer Injectables

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