PRODUCT MONOGRAPH

# Pr GEMCITABINE INJECTION

**Concentrate Sterile Solution for Injection**

**Gemcitabine (as Gemcitabine Hydrochloride)**

**40 mg gemcitabine per mL**

**200 mg/5 mL, 1 g/25 mL, 2 g/50 mL**

**Antineoplastic Agent**

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Sterile

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Intravenous | Solution /200 mg/5 mL, 1 g/25 mL, 2 g/50 mL per vial | For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section. |

### INDICATIONS AND CLINICAL USE

Gemcitabine Injection is indicated for the:

- Treatment of patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas to achieve a Clinical Benefit Response (a composite measure of clinical improvement).
- Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) as either a single agent or in combination with cisplatin.
- Treatment of patients with Stage IV (locally advanced or metastatic) transitional cell carcinoma (TCC) of the bladder in combination with cisplatin.
- Treatment, in combination with paclitaxel, of patients with unresectable, locally recurrent or metastatic breast cancer, who have good performance status and have relapsed following adjuvant anthracycline-based chemotherapy.

Gemcitabine Injection should be used only under the supervision of a qualified healthcare professional who is experienced in the use of chemotherapeutic agents and in the management of patients with cancer. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

**Geriatrics (>65 years of age)**
Gemcitabine hydrochloride has been well tolerated in patients over the age of 65. Although clearance is affected by age (see ACTION AND CLINICAL PHARMACOLOGY), there is no evidence that further dose adjustments, (i.e. other than those already recommended in the DOSAGE AND ADMINISTRATION) are necessary in patients over the age of 65.

**Pediatrics (<17 years of age)**
Safety and effectiveness in children have not been established.

## CONTRAINDICATIONS

Gemcitabine Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING in the Product Monograph.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- Gemcitabine Injection is a cytotoxic drug and should be used only by physicians experienced with chemotherapeutic drugs. Patients should be informed of the risks associated with Gemcitabine Injection therapy.
- Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity (see DOSAGE AND ADMINISTRATION, and Part II: CLINICAL TRIALS).
- Gemcitabine Injection should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from previous chemotherapy.
- Gemcitabine Injection can suppress bone marrow function manifested by leucopenia, thrombocytopenia and anemia. Patients should be closely monitored prior to each dose for granulocyte and platelet counts. The dosage should be reduced, omitted, or the drug discontinued upon evidence of abnormal suppression of the bone marrow (see DOSAGE AND ADMINISTRATION).
- Periodic physical examination and checks of renal and hepatic function should be made to detect non-hematologic toxicity. Doses may be reduced or withheld based upon the level of toxicity.
- Administration of Gemcitabine Injection in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency (see DOSAGE AND ADMINISTRATION).
- Acute shortness of breath with a temporal relationship to Gemcitabine Injection administration may occur (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).
- This preparation is for intravenous administration only.

### General

In all instances where the use of Gemcitabine Injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. If severe adverse events occur, the drug should be reduced in dosage, omitted, or discontinued and appropriate corrective measures should be taken based on the clinical judgement of the physician (see DOSAGE AND ADMINISTRATION).

Most drug-related adverse reactions observed with gemcitabine hydrochloride therapy are reversible (see ADVERSE REACTIONS).

**Carcinogenesis and Mutagenesis**
Information available is based upon pre-clinical studies (see TOXICOLOGY).

**Cardiovascular**
Heart failure has been reported very rarely (<0.01%). Arrhythmias, predominantly supraventricular in nature, have been reported signaling awareness of the possibility of cardiovascular events (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions Post-Market Adverse Drug Reactions and).

**Fever or Flu-like Symptoms**
Gemcitabine hydrochloride may cause fever, with or without flu-like symptoms, in the absence of clinical infection (see ADVERSE REACTIONS). The administration of acetaminophen may provide symptomatic relief.

**Hematologic**
Gemcitabine hydrochloride can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia. Blood counts should be taken prior to each dose (see DOSAGE AND ADMINISTRATION for dose reduction guidelines).

**Hepatic**
Cases of serious hepatotoxicity including liver failure and death have been very rarely reported in patients receiving gemcitabine hydrochloride alone or in combination with other potentially hepatotoxic drugs. A causal relationship between gemcitabine hydrochloride and severe hepatotoxicity including liver failure and death has not been established (see WARNINGS AND PRECAUTIONS, Special Populations, and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions and Post-Market Adverse Drug Reactions).

**Nervous System**
Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported very rarely (<0.01%) in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents, including platinum-containing agents. Acute hypertension and seizure activity were reported in most patients. The onset of PRES signs and symptoms was reported to occur from a few days to six months after initiation of gemcitabine. PRES was typically reversible in these patients. PRES can present with headache, hypertension, seizure, lethargy, confusion, blindness, and other visual and neurologic disturbances. Diagnosis is optimally confirmed by magnetic resonance imaging. Gemcitabine Injection should be permanently discontinued, and supportive measures, including blood pressure control and anti-seizure therapy, should be implemented if PRES develops during therapy (WARNINGS AND PRECAUTIONS: Vascular section; ADVERSE REACTIONS: Post-Market Adverse Drug Reactions section).

**Radiosensitizing Effect**
In a single trial where gemcitabine hydrochloride at a dose of 1 000 mg/m$^2$ was administered once weekly for up to six (6) consecutive weeks concurrently with therapeutic thoracic radiation to patients with NSCLC, significant toxicity was observed in the form of severe, and potentially life-threatening mucositis, especially esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4 795 cm$^3$] (see DRUG

INTERACTIONS for more information). The optimum regimen for safe administration of gemcitabine hydrochloride with therapeutic doses of radiation has not yet been determined.

**Renal**

There have been cases of histologically confirmed Hemolytic Uremic Syndrome (HUS) reported uncommonly (0.25% in clinical trials) in patients treated with gemcitabine hydrochloride. Renal failure leading to death or requiring dialysis despite discontinuation of therapy has been reported rarely. The majority of cases of renal failure leading to death were due to HUS (see WARNINGS AND PRECAUTIONS, Special Populations; Vascular section and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions and Post-Market Adverse Drug Reactions sections).

Gemcitabine Injection should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible even with discontinuation of therapy, and dialysis may be required.

**Respiratory**

Acute shortness of breath in association with gemcitabine hydrochloride administration may occur. Bronchodilators, corticosteroids, and/or oxygen produce symptomatic relief.

Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS)) have been reported rarely (<0.1%) in association with gemcitabine hydrochloride therapy, some of which may be attributed to capillary leak syndrome (see Vascular section below). If such effects develop, patients should discontinue therapy with Gemcitabine Injection and not be re-challenged with the drug. See WARNINGS AND PRECAUTIONS: Vascular section; ADVERSE REACTIONS, Pulmonary and DOSAGE AND ADMINISTRATION sections.

**Skin**

Gemcitabine hydrochloride administration has been associated with rash (see ADVERSE REACTIONS). Topical corticosteroids may provide symptomatic relief.

Severe skin reactions, including desquamation and bullous skin eruptions such as toxic epidermal necrolysis (TEN) and Stevens Johnson syndrome (SJS), have been reported very rarely (<0.01%).

**Vascular**

Clinical signs of peripheral vasculitis and gangrene and capillary leak syndrome have been reported very rarely (<0.01%) in association with gemcitabine hydrochloride therapy.

Reports of capillary leak syndrome (CLS) with potentially severe consequences have been reported in patients receiving gemcitabine hydrochloride as single agent or in combination with other chemotherapeutic agents. Gemcitabine hydrochloride should be permanently discontinued and supportive measures implemented if CLS develops during therapy (see ADVERSE DRUG REACTIONS: Post-Market Adverse Drug Reactions, Vascular section).

Reports of hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), adult respiratory distress syndrome (ARDS), and posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as single agent or in combination with other chemotherapeutic agents. These events can be related to vascular endothelial injury possibly induced by gemcitabine. Gemcitabine should be discontinued and supportive measures implemented if any of these develop during therapy (see Nervous System, Renal, Respiratory sections above: and ADVERSE REACTIONS).

**Special Populations**

**Gender:** Gemcitabine hydrochloride clearance is affected by gender (see ACTION AND CLINICAL PHARMACOLOGY). There is no evidence, however, that further dose adjustments (i.e. other than those already recommended in the DOSAGE AND ADMINISTRATION) are necessary in women.

**Renal and Hepatic Impairment:** Gemcitabine Injection should be used with caution in patients with pre-existing renal or hepatic insufficiency, as there is insufficient information from clinical studies to allow clear dose recommendations for this patient population. All combination studies involving gemcitabine hydrochloride and cisplatin have been performed in patients with creatinine clearance of ≥60 mL/minute.

Administration of gemcitabine hydrochloride in patients with compromised liver function due to liver metastasis or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

**Pregnant Women:** The use of Gemcitabine Injection should be avoided in pregnant women because of the potential hazard to the fetus. Evaluation of experimental animal studies has shown reproductive toxicity, e.g. birth defects or other effects on the development of the embryo or fetus, the course of gestation or peri- and postnatal development.

**Nursing Women:** The use of Gemcitabine Injection should be avoided in nursing women because of the potential hazard to the infant.

**Pediatrics (<17 years of age):** Safety and effectiveness in children have not been established.

**Geriatrics (>65 years of age):** Gemcitabine hydrochloride has been well tolerated in patients over the age of 65. Although clearance is affected by age (see ACTION AND CLINICAL PHARMACOLOGY), there is no evidence that further dose adjustments, (i.e. other than those recommended under DOSAGE AND ADMINISTRATION) are necessary in patients over the age of 65.

## ADVERSE REACTIONS

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and*

*should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Gemcitabine hydrochloride has been used, both as a single agent and in combination with other cytotoxic drugs.

**Single-Agent Use:** Data in Table 1 are based on 22 clinical studies (N=979) of gemcitabine hydrochloride administered as a single agent, using starting doses in the range of 800 to 1 250 $mg/m^2$ administered weekly as a 30-minute infusion for the treatment of a wide variety of malignancies. Of the 979 patients only 10.4% (102) were discontinued due to an adverse event regardless of causality. WHO grade 3 or 4 toxicity of non-laboratory events, was less than 1% for all parameters except nausea and vomiting, pulmonary toxicity, infection and pain.

All WHO-graded laboratory toxicities for a total of 979 patients are listed in Table 1, regardless of causality. Non-laboratory WHO-toxicities were available for 565 patients. They are listed in Table 1 (for parameters that occurred in ≥5% of patients), or discussed below. Edema, extravasation and flu-like symptoms were reported regardless of causality as treatment-emergent signs and symptoms (TESS[1]; N=979).

Data are also shown (Table 1) for the subset of patients (N=360) with non-small cell lung cancer treated in 4 clinical studies (2 studies WHO laboratory toxicities; 2 studies non-laboratory

WHO-toxicities) and the subset of patients (N=159) with pancreatic cancer treated in 5 clinical studies (WHO laboratory and non-laboratory toxicities). The frequency of all grades were generally similar for the overall safety database and the subsets of patients with non-small cell lung cancer and pancreatic cancer.

[1] TESS: An event was considered treatment-emergent, if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that although the events were reported during therapy, they were not necessarily caused by the therapy.

**Table 1:** WHO-Graded Toxicities Occurring with a ≥5 % Frequency in Patients Receiving Gemcitabine Hydrochloride.

| WHO Grades (in % frequency) are rounded to the closest integer | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **All Patients** | | | **Non-Small Cell Lung Cancer Patients** | | | **Pancreatic Cancer Patients** | | | **Discontinu-ations (%)** |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 | **All Patients** |
| **LABORATORY** | **(N=979)** | | | **(N=360)** | | | **(N=244)** | | | **(N=979)** |
| **Hematologic** | | | | | | | | | | |
| Anemia | 68 | 7 | 1 | 65 | 5 | <1 | 73 | 8 | 3 | <1 |
| Neutropenia | 63 | 19 | 6 | 61 | 20 | 5 | 61 | 17 | 7 | |
| Leukopenia | 62 | 9 | <1 | 55 | 7 | <1 | 63 | 8 | 1 | <1 |
| Thrombocytopenia | 24 | 4 | 1 | 16 | 1 | 1 | 36 | 7 | <1 | <1 |
| **Hepatic** | | | | | | | | | | |
| ALT | 68 | 8 | 2 | 70 | 9 | 3 | 72 | 10 | 1 | <1 |
| AST | 67 | 7 | 2 | 67 | 5 | 1 | 78 | 12 | 5 | |
| Alkaline Phosphatase | 55 | 7 | 2 | 48 | 2 | 0 | 77 | 16 | 4 | |
| Bilirubin | 13 | 2 | <1 | 8 | <1 | <1 | 26 | 6 | 3 | |
| **Renal** | | | | | | | | | | |
| Proteinuria | 36 | <1 | 0 | 52 | <1 | 0 | 15 | <1 | 0 | |
| Hematuria | 31 | <1 | 0 | 43 | 2 | 0 | 14 | 0 | 0 | |
| BUN | 16 | 0 | 0 | 16 | 0 | 0 | 15 | 0 | 0 | <1 |
| Creatine | 7 | <1 | 0 | 6 | <1 | 0 | 6 | 0 | 0 | |
| **NON-LABORATORY** | **(N=565)** | | | **(N=243)** | | | **(N=159)** | | | **(N=979)** |
| **Gastrointestinal Disorders** | | | | | | | | | | |
| Nausea and vomiting | 64 | 17 | 1 | 69 | 19 | <1 | 62 | 12 | 2 | <1 |
| Diarrhea | 12 | <1 | 0 | 6 | <1 | 0 | 24 | 2 | 0 | 0 |
| Constipation | 8 | <1 | 0 | 7 | <1 | 0 | 13 | 2 | 0 | 0 |
| Stomatitis | 8 | <1 | 0 | 7 | <1 | 0 | 10 | 0 | 0 | <1 |
| **General Disorders and Administration Site Conditions** | | | | | | | | | | |
| Fever | 37 | <1 | 0 | 46 | <1 | 0 | 28 | <1 | 0 | <1 |
| Pain | 16 | 1 | 0 | 16 | 1 | 0 | 12 | 2 | 0 | <1 |
| **Infections** | | | | | | | | | | |
| Infection | 9 | 1 | <1 | 10 | 0 | 0 | 8 | 1 | 0 | <1 |
| **Nervous System Disorders** | | | | | | | | | | |
| State of consciousness/Somnolence | 9 | <1 | 0 | 6 | 0 | 0 | 10 | 3 | 0 | <1 |
| **Respiratory Disorders** | | | | | | | | | | |
| Dyspnea | 8 | 1 | <1 | 8 | 2 | 0 | 6 | 0 | 0 | <1 |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | | | | | |
| Skin Rash | 25 | <1 | 0 | 30 | 0 | 0 | 22 | 0 | 0 | <1 |
| Alopecia | 14 | <1 | 0 | 14 | <1 | 0 | 14 | 0 | 0 | 0 |

Grades based on criteria from the World Health Organization (WHO).

## Alopecia

Hair loss (alopecia), usually minimal, was reported for any WHO grade in only 13.7% of patients. No grade 4 toxicity (non-reversible alopecia) was reported, and only 0.4% of patients reported grade 3 toxicity (complete but reversible alopecia).

## Cardiac Toxicity

Less than two percent of patients discontinued therapy with gemcitabine hydrochloride due to cardiovascular events such as myocardial infarction, arrhythmia, chest pain, heart failure,

pulmonary edema and hypertension. Many of these patients had a prior history of cardiovascular disease.

**Cutaneous Toxicity**
A rash was seen in 24.8% of patients, was usually mild, not dose limiting and responded to local therapy (see WARNINGS AND PRECAUTIONS). The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities.

**Edema**
The occurrence of edema is reported regardless of causality, as a treatment-emergent event (TESS). Edema (13%), peripheral edema (20%) and facial edema (<1%) were reported. Overall, edema was usually mild to moderate and reversible. Less than 1% of patients (N=979) discontinued due to edema.

**Extravasation**
Gemcitabine hydrochloride is well tolerated during the infusion with only a few cases (4%) of injection site reaction reported. Gemcitabine hydrochloride does not appear to be a vesicant (see DOSAGE AND ADMINISTRATION). There have been no reports of injection site necrosis.

**Fever and Infection**
Fever of any severity was reported in 37.3% of patients. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable. Less than 1% of patients were discontinued for fever. The incidence of fever contrasts with the incidence of infection (8.7%) and indicates that gemcitabine hydrochloride may cause fever in the absence of clinical infection (see WARNINGS AND PRECAUTIONS).

**Flu-Like Symptoms**
"Flu-syndrome" was reported regardless of causality (TESS) for 18.9% of patients (N=979). Individual symptoms of headache, anorexia, fever, chills, myalgia and asthenia were the most commonly reported symptoms. Cough, rhinitis, malaise, sweating and insomnia were also commonly reported. Less than 1% of patients discontinued due to flu-like symptoms.

**Gastrointestinal**
Mild or moderate nausea and vomiting (WHO toxicity grade 1 and 2) was reported in 64% of all patients. WHO grade 3 toxicity, defined as vomiting requiring therapy, was reported in 17.1% of patients. Any patient, who received prophylactic antiemetics, was automatically graded ≥WHO grade 3, even if they only developed mild nausea. Diarrhea and stomatitis were usually mild and occurred in less than 13% of patients. WHO toxicity for constipation was mild (WHO grade 1) in the majority of cases and was reported for 7.8% of patients.

**Hematologic**
Myelosuppression is the major dose-limiting toxicity with gemcitabine hydrochloride; it was usually of short duration, reversible and not cumulative over time. Less than 1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were received by 19% of patients and less than 1% of patients received platelet

transfusions. The incidence of major infection (WHO-grade toxicity of 3) was only 1.1% and only one grade 4 toxicity for infection occurred.

**Hepatic**
Gemcitabine hydrochloride was associated with transient elevations of serum transaminases (predominantly WHO grades 1 and 2) in approximately two-thirds of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of treatment with gemcitabine hydrochloride or with greater total cumulative dose.

**Neurotoxicity**
WHO grade 1 or 2 peripheral neurotoxicity[2] was reported for 3.3% of patients. No patient reported WHO grade 3 or 4 toxicity.

State of consciousness toxicity was usually mild to moderate (WHO grades 1 and 2); somnolence was reported for 4.6% of patients.

**Pulmonary and Allergic**
Gemcitabine hydrochloride should not be administered to patients with a known hypersensitivity to this drug. One case of anaphylactoid reaction has been reported.

The administration of gemcitabine hydrochloride has been infrequently associated with shortness of breath (Dyspnea; see WARNINGS AND PRECAUTIONS). Dyspnea when graded by WHO-toxicity criteria (Table 1), was reported in 8%, and severe dyspnea (WHO grades 3 and 4) was reported in 1.4% of patients.

Dyspnea, regardless of causality (TESS) was reported in 23% of patients and serious dyspnea was reported in 3% of patients. It should be noted that in both of these analyses, the occurrence of dyspnea may have been due to underlying disease such as lung cancer (40% of study population) or pulmonary manifestations of other malignancies. Dyspnea was occasionally accompanied by bronchospasm (<1% of patients).

**Renal**
Mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) were reported in 6 out of 2 429 patients (0.25%) receiving gemcitabine hydrochloride in clinical trials (see WARNINGS AND PRECAUTIONS). Renal failure associated with HUS, may not be reversible even with discontinuation of therapy and dialysis may be required.

**Combination Use with Cisplatin in Non-Small Cell Lung Cancer:** This section focuses on adverse events that were increased in frequency and/or severity with the addition of cisplatin to gemcitabine hydrochloride. Gemcitabine hydrochloride plus cisplatin was compared to single-agent cisplatin in a randomized trial, and safety data were collected using NCI Common Toxicity Criteria (CTC). In a second randomized trial, gemcitabine hydrochloride plus cisplatin was compared to the combination of cisplatin plus etoposide, and World Health Organization (WHO)

[2] WHO grade 1 peripheral neurotoxicity is defined as paresthesia and/or decreased tendon reflexes and WHO grade 2 is defined as severe paresthesia and/or mild weakness.

criteria were used to grade adverse reactions. All CTC- and WHO-graded adverse events that occurred in ≥10% of patients are listed in Table 2. Toxicity grades for laboratory parameters are reported regardless of causality.

**Table 2:** CTC- and WHO-Graded Toxicities Occurring with a ≥10% Frequency in NSCLC Patients Receiving Gemcitabine Hydrochloride plus Cisplatin.

| CTC and WHO Grades (in % frequency) are rounded to the closest integer | | | | | | | |
|---|---|---|---|---|---|---|---|
| **NCI COMMON TOXICITY CRITERIA** | **Gemcitabine Hydrochloride plus Cisplatin (N=260) [a] *vs* Cisplatin (N=262) (% incidence)** | | | **WORLD HEALTH ORGANIZATION CRITERIA** | **Gemcitabine Hydrochloride plus Cisplatin (N=69) [a] *vs* Cisplatin plus Etoposide (N=66) (% incidence)** | | |
| | All Grades | Grade 3 | Grade 4 | | All Grades | Grade 3 | Grade 4 |
| **LABORATORY [c]** | | | | | | | |
| **Hematologic** | | | | | | | |
| Anemia | 89 | 22 | 3 | Anemia | 88 | 22 | 0 |
| Thrombocytopenia | 85 | 25 | 25 | Thrombocytopenia | 81 | 39 | 16 |
| Leukopenia | 82 | 35 | 11 | Leukopenia | 86 | 26 | 3 |
| Neutropenia | 79 | 22 | 35 | Neutropenia | 88 | 36 | 28 |
| Lymphocytes | 75 | 25 | 18 | | | | |
| **Hepatic** | | | | | | | |
| Transaminase | 22 | 2 | 1 | | | | |
| Alkaline Phosphatase | 19 | 1 | 0 | Alkaline Phosphatase | 16 | 0 | 0 |
| **Renal** | | | | | | | |
| Creatinine | 38 | 4 | <1 | | | | |
| Proteinuria | 23 | 0 | 0 | Proteinuria | 12 | 0 | 0 |
| Hematuria | 15 | 0 | 0 | Hematuria | 22 | 0 | 0 |
| **Other Laboratory** | | | | | | | |
| Hypomagnesemia | 30 | 4 | 3 | | | | |
| Hyperglycemia | 30 | 4 | 0 | | | | |
| Hypocalcemia | 18 | 2 | 0 | | | | |
| **NON-LABORATORY[d]** | | | | | | | |
| **Blood** | | | | | | | |
| Hemorrhage | 14 | 1 | 0 | | | | |
| **Gastrointestinal Disorders** | | | | | | | |
| Nausea | 93 | 25 | 2 | Nausea and Vomiting | 96 | 35 | 4 |
| Vomiting | 78 | 11 | 12 | | | | |
| Constipation | 28 | 3 | 0 | Constipation | 17 | 0 | 0 |
| Diarrhea | 24 | 2 | 2 | Diarrhea | 14 | 1 | 1 |
| Stomatitis | 14 | 1 | 0 | Stomatitis | 20 | 4 | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | | |
| Fever | 16 | 0 | 0 | | | | |
| Local | 15 | 0 | 0 | | | | |
| **Infections** | | | | | | | |
| Infections | 18 | 3 | 2 | Infections | 28 | 3 | 1 |
| **Nervous System Disorders** | | | | | | | |
| Neuro-motor | 35 | 12 | 0 | Paresthesias | 38 | 0 | 0 |
| Neuro-hearing | 25 | 6 | 0 | | | | |
| Neuro-sensory | 23 | 1 | 0 | | | | |
| Neuro-cortical | 16 | 3 | 1 | | | | |
| Neuro-mood | 16 | 1 | 0 | | | | |
| Neuro-headache | 14 | 0 | 0 | | | | |
| **Respiratory Disorders** | | | | | | | |
| Dyspnea | 12 | 4 | 3 | | | | |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | | |
| Alopecia | 53 | 1 | 0 | Alopecia | 77 | 13 | 0 |
| Rash | 11 | 0 | 0 | Rash | 10 | 0 | 0 |
| **Vascular Disorders** | | | | | | | |

**Table 2:** CTC- and WHO-Graded Toxicities Occurring with a ≥10% Frequency in NSCLC Patients Receiving Gemcitabine Hydrochloride plus Cisplatin.

| **CTC and WHO Grades (in % frequency) are rounded to the closest integer** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **NCI COMMON TOXICITY CRITERIA** | **Gemcitabine Hydrochloride plus Cisplatin (N=260) [a] *vs* Cisplatin (N=262) (% incidence)** | | | **WORLD HEALTH ORGANIZATION CRITERIA** | **Gemcitabine Hydrochloride plus Cisplatin (N=69) [a] *vs* Cisplatin plus Etoposide (N=66) (% incidence)** | | |
| | All Grades | Grade 3 | Grade 4 | | All Grades | Grade 3 | Grade 4 |
| Hypotension | 12 | 1 | 0 | | | | |

[a] Gemcitabine hydrochloride plus cisplatin patients with laboratory or non-laboratory data, N=217-253. Gemcitabine hydrochloride at 1 000 mg/m$^2$ on Days 1, 8 and 15 and cisplatin at 100 mg/m$^2$ on Day 1 every 28 days.
[b] Gemcitabine hydrochloride plus cisplatin patients with laboratory or non-laboratory data, N=67-69. Gemcitabine hydrochloride at 1 250 mg/m$^2$ on Days 1 and 8 and cisplatin at 100 mg/m$^2$ on Day 1 every 21 days.
[c] Regardless of causality.
[d] Non-laboratory events were graded only if assessed to be possibly drug-related.

### Alopecia

In comparison with single-agent gemcitabine hydrochloride therapy, the incidence of alopecia with gemcitabine hydrochloride plus cisplatin combination therapy was increased; 14% with gemcitabine hydrochloride alone *versus* 53% and 77% with gemcitabine hydrochloride plus cisplatin. Hair loss was usually minimal (CTC/WHO Grade 1 or 2). However, 0.8% of patients that received gemcitabine hydrochloride plus cisplatin on the 4-week schedule experienced CTC Grade 3 alopecia, and 13% of patients who were on the 3-week schedule experienced WHO Grade 3 alopecia. No irreversible (i.e. Grade 4) hair loss was reported.

### Fever and Infection

The majority of patients that received gemcitabine hydrochloride plus cisplatin did not develop fever and only one patient (4-week cycle) experienced CTC Grade 3 fever. On the 4-week gemcitabine hydrochloride plus cisplatin schedule, CTC Grade 3 and 4 infection was seen in 2.8% and 1.6% of patients, respectively. On the 3-week schedule, WHO Grade 3 and 4 infection was seen in 2.9% and 1.4% of patients, respectively.

### Gastrointestinal

The incidence of nausea and vomiting was higher for combination therapy with gemcitabine hydrochloride plus cisplatin (~90%) than it was for single agent gemcitabine hydrochloride (50-70%). On the 4-week cycle, 23% of patients in the gemcitabine hydrochloride plus cisplatin arm experienced CTC Grade 3 or Grade 4 nausea and vomiting, and on the 3-week cycle, the incidence of WHO Grade 3 or 4 nausea and vomiting was 39.1% in the gemcitabine hydrochloride plus cisplatin arm, despite the use of antiemetics. Although nausea and vomiting were frequent, they were rarely dose-limiting and were seldom reasons for discontinuation from the study. Diarrhea, stomatitis and constipation were usually mild and occurred in 14-28% of patients that received gemcitabine hydrochloride plus cisplatin.

### Hematologic

As expected, myelosuppression occurred more frequently with gemcitabine hydrochloride plus cisplatin treatment (~90%) than with gemcitabine hydrochloride monotherapy (~60%), and gemcitabine hydrochloride dosage adjustments for hematologic toxicity were required more often

with combination therapy. Although myelosuppression was common, early study discontinuation due to bone marrow suppression occurred in only 3.1% and 4.3% of patients receiving gemcitabine hydrochloride plus cisplatin in the two randomized trials. Platelet transfusions were required by 3% and 21% of patients that received gemcitabine hydrochloride plus cisplatin on a 3-week or 4-week cycle, respectively, and red blood cell transfusions were required by approximately 30-40% of patients. Less than 8% of patients treated with gemcitabine hydrochloride plus cisplatin were hospitalized for febrile neutropenia. Sepsis and severe hemorrhagic events were rare.

**Neurotoxicity**
CTC Grade 3 neuro-hearing toxicity (hearing loss interfering with function but correctable with hearing aid) was experienced by 5.6% and 2.9% of gemcitabine hydrochloride plus cisplatin patients on 4-week and 3-week schedules, respectively. CTC Grade 3 neuromotor toxicity was experienced by 11.5% of gemcitabine hydrochloride plus cisplatin patients on the 4-week schedule, and 38% of patients on the 3-week schedule experienced peripheral neurotoxicity (WHO Grade 1 or 2 only).

**Renal**
On the 4-week gemcitabine hydrochloride plus cisplatin schedule, CTC Grade 3 creatinine toxicity was observed in 4.4% of patients, and one patient experienced Grade 4 creatinine toxicity. On the 3-week schedule, no WHO Grade 2, 3 or 4 BUN or creatinine toxicity were observed.

**Combination Use with Cisplatin in Bladder Cancer [Transitional Cell Carcinoma (TCC) of the Urothelium]:** The following information presents adverse events seen with gemcitabine hydrochloride in combination with cisplatin for treatment of bladder cancer. Gemcitabine hydrochloride plus cisplatin (GC) was compared to MVAC in a pivotal, randomized trial.

Safety data were collected using the WHO-toxicity criteria with the exception of neurohearing event which was graded using the NCI Common Toxicity Criteria. All WHO- and CTC-graded adverse events that occurred in ≥10% of patients are listed in Table 3.

**Alopecia**
Grade 3 and 4 alopecia occurred significantly less often in gemcitabine hydrochloride plus cisplatin patients than in MVAC patients (GC 10.5% *vs* 55.2%).

**Cardiac**
Grade 3 and 4 cardiovascular events such as myocardial function, arrhythmia, chest pain, heart failure, pulmonary edema and hypertension were rare; Grade 3 events occurred in 4.1% of patients on gemcitabine hydrochloride plus cisplatin. There were no Grade 4 events. In the MVAC arm 2.2% of patients experienced Grade 3 events and 0.5% of patients experience Grade 4 events.

**Gastrointestinal**
The incidence of diarrhea was higher in the MVAC treatment arm than it was for the gemcitabine hydrochloride plus cisplatin. In the MVAC arm, 8% of patients experienced Grade 3 or 4 diarrhea compared to 3% of patients in the gemcitabine hydrochloride plus cisplatin arm. Nausea and

vomiting occurred in similar frequencies among the gemcitabine hydrochloride plus cisplatin (22%) and the MVAC arms (21%).

**Hematologic**
Hematologic toxicity was the most frequent laboratory toxicity seen on both treatment arms in this pivotal trial. Grade 3 and 4 neutropenia occurred less often in gemcitabine hydrochloride plus cisplatin patients than in MVAC patients (GC 71% *vs* MVAC 82%). Grade 3 and 4 anemia was more common on the gemcitabine hydrochloride plus cisplatin arm *versus* MVAC arm (27% *vs* 18%). Grade 3 and 4 thrombocytopenia was more common on the gemcitabine hydrochloride plus cisplatin arm *versus* MVAC arm (GC 57% *vs* MVAC 21%). In patients with Grade 3 or 4 thrombocytopenia there was no Grade 4 bleeding and only infrequent Grade 3 bleeding (<2%) on either arm. On the gemcitabine hydrochloride plus cisplatin arm, for every 100 cycles of chemotherapy, 13 patients received whole blood or red blood cell transfusion. On the MVAC arm, for every 100 cycles of chemotherapy, 13 patients received whole blood or red blood cell transfusion. On the gemcitabine hydrochloride plus cisplatin arm, for every 100 cycles of chemotherapy, 4 patients received platelet transfusion. On the MVAC arm, for every 100 cycles of chemotherapy, 2 patients received platelet transfusion.

**Neurotoxicity**
Of the 191 patients assessed in the gemcitabine hydrochloride plus cisplatin arm, CTC Grade 3 neuro-hearing toxicity occurred in 3 patients (2%). No patient experienced Grade 4 neuro-hearing toxicity. By comparison, out of 173 patients assessed in the MVAC arm, CTC Grade 3 neuro-hearing toxicity occurred in 3 patients. Grade 4 neuro-hearing toxicity occurred in 1 patient.

**Pulmonary**
Grade 3 and 4 dyspnea occurred in 2.5% and 0.5% of patients on the gemcitabine hydrochloride plus cisplatin respectively, while compared to 2.6% Grade 3 and 3.1% Grade 4 dyspnea in the MVAC arm.

**Renal**
No patients on the gemcitabine hydrochloride plus cisplatin arm experienced Grade 3 or 4 renal toxicity, while Grade 3 renal toxicity was observed in 0.5% of patients in the MVAC arm. Renal toxicity was measured by serum creatinine levels.

**Table 3:** Selected WHO-Graded Adverse Events from Comparative Trial of Gemcitabine Hydrochloride plus Cisplatin *versus* MVAC in TCC of the Bladder

| WHO Grades (% incidence) | | | | | | |
|---|---|---|---|---|---|---|
| | **Gemcitabine Hydrochloride plus Cisplatin [a]** | | | **MVAC [b]** | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| **LABORATORY [c]** | | | | | | |
| **Hematologic** | | | | | | |
| Anemia | 94 | 24 | 4 | 86 | 16 | 2 |
| Leukopenia | 92 | 44 | 7 | 93 | 46 | 18 |
| Neutropenia | 91 | 41 | 30 | 89 | 17 | 65 |
| Thrombocytopenia | 86 | 29 | 29 | 46 | 8 | 13 |
| Platelet Transfusions[d] | 18 | | | 8 | | |
| **Hepatic** | | | | | | |
| AST | 30 | 1 | 0 | 28 | 2 | 0 |
| ALT | 29 | 1 | 0 | 28 | 2 | 0 |
| Alkaline Phosphatase | 17 | 2 | 1 | 19 | 1 | 0 |
| **Renal** | | | | | | |
| BUN | 36 | 1 | 0 | 37 | 0 | 0 |
| Creatinine | 24 | 0 | 0 | 23 | 1 | 0 |
| Hematuria | 18 | 5 | 0 | 21 | 2 | 0 |
| Proteinuria | 9 | 0 | 0 | 14 | 1 | 0 |
| **NON-LABORATORY[e]** | | | | | | |
| **Blood** | | | | | | |
| Hemorrhage | 23 | 2 | 0 | 15 | 2 | 0 |
| **Gastrointestinal Disorders** | | | | | | |
| Nausea and Vomiting | 78 | 22 | 0 | 86 | 19 | 2 |
| Constipation | 38 | 2 | 0 | 39 | 3 | 1 |
| Diarrhea | 24 | 3 | 0 | 34 | 8 | 1 |
| Stomatitis | 20 | 1 | 0 | 66 | 18 | 4 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fever | 21 | 0 | 0 | 30 | 3 | 0 |
| **Infections** | | | | | | |
| Infections | 24 | 2 | 1 | 47 | 10 | 5 |
| **Nervous System Disorders** | | | | | | |
| Paresthesias | 26 | 1 | 0 | 25 | 1 | 0 |
| Neuro-Hearing [f] | 19 | 2 | 0 | 14 | 2 | 1 |
| Somnolence | 17 | 1 | 0 | 30 | 3 | 1 |
| **Respiratory Disorders** | | | | | | |
| Dyspnea | 28 | 3 | 1 | 21 | 3 | 3 |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | |
| Alopecia | 61 | 11 | 0 | 89 | 54 | 1 |
| Rash | 23 | 0 | 0 | 16 | 0 | 1 |

Grades based on criteria from the World Health Organization (WHO).

[a] N=191-200; all patients on gemcitabine hydrochloride plus cisplatin with laboratory or non-laboratory data; gemcitabine hydrochloride 1 000 mg/m$^2$ on Days 1, 8 and 15 and cisplatin 70 mg/m$^2$ on Day 2 of each 28-day cycle.

[b] N=186-194; all patients on MVAC with laboratory or non-laboratory data: methotrexate 30 mg/m$^2$ on Days 1, 15 and 22, vinblastine 3 mg/m$^2$ on Days 2, 15 and 22, doxorubicin 30 mg/m$^2$ on Day 2 and cisplatin 70 mg/m$^2$ on Day 2 of each 28-day cycle.

[c] Regardless of causality .

[d] Percent of patients requiring transfusion.

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

[f] Grade based on NCI Common Toxicity Criteria.

**Combination Use with Paclitaxel in Breast Cancer**
The following information presents adverse events seen with gemcitabine hydrochloride in combination with paclitaxel for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following anthracycline-based chemotherapy. Gemcitabine hydrochloride plus paclitaxel was compared to paclitaxel in Study JHQG, an unblinded, multicentre, randomized Phase 3 study.

In the gemcitabine hydrochloride plus paclitaxel arm, 7% of patients discontinued treatment because of an adverse event compared to 5% on the paclitaxel arm. In the gemcitabine hydrochloride plus paclitaxel arm, 7% of gemcitabine hydrochloride doses were omitted and 8% were reduced, and 0.9% of paclitaxel doses were omitted and 5% were reduced. In the paclitaxel alone arm, 0.1% of paclitaxel doses were omitted and 2% were reduced. There were 12 deaths in the gemcitabine hydrochloride plus paclitaxel arm, and 8 in the paclitaxel alone arm on study or within 30 days after study drug discontinuation. One death on each arm of the study was possibly drug-related, while the rest of the deaths were attributed to progressive disease and a single death attributed to a traffic accident.

The hospitalization of patients in the gemcitabine hydrochloride plus paclitaxel arm and in the paclitaxel alone arm were similar and not statistically significant (8.8% and 7.3%, respectively). Median number of cycles given in the gemcitabine hydrochloride plus paclitaxel arm was 6, compared with 5 cycles given in the paclitaxel alone arm.

Table 4 presents a summary of Grade 3 and 4 toxicities reported in the pivotal clinical study JHQG.

**Table 4:** Percentages of Patients with Grade 3 and 4 Toxicities Reported in the Clinical Study of Gemcitabine Hydrochloride in Combination with Paclitaxel in Patients with Metastatic Breast Cancer

| CTC Grades (% incidence, rounded to the closest integer) [a] | | | | | | |
|---|---|---|---|---|---|---|
| | Gemcitabine Hydrochloride plus Paclitaxel (N=262) | | | Paclitaxel Alone (N=259) | | |
| | All Grades | Grade 3 | Grade 4 | All Grades | Grade 3 | Grade 4 |
| **LABORATORY [b]** | | | | | | |
| **Hematologic** | | | | | | |
| Neutropenia | 69 | 31 | 17 | 31 | 4 | 7 |
| Anemia | 69 | 6 | 1 | 51 | 3 | <1 |
| Thrombocytopenia | 26 | 5 | <1 | 7 | <1 | <1 |
| Leukopenia | 21 | 10 | 1 | 12 | 2 | 0 |
| **Liver Abnormalities** | | | | | | |
| ALT | 18 | 5 | <1 | 6 | <1 | 0 |
| AST | 16 | 2 | 0 | 5 | <1 | 0 |
| **Metabolic** | | | | | | |
| Hyperglycemia | 6 | 3 | 0 | 5 | 3 | 0 |
| **NON-LABORATORY[c]** | | | | | | |
| **Cardiac Disorders** | | | | | | |
| Arrhythmia | <1 | <1 | 0 | 0 | 0 | 0 |
| **Gastrointestinal Disorders** | | | | | | |
| Nausea | 50 | 1 | 0 | 31 | 2 | 0 |
| Vomiting | 29 | 2 | 0 | 15 | 2 | 0 |
| Diarrhea | 20 | 3 | 0 | 13 | 2 | 0 |
| Stomatitis/Pharyngitis | 13 | 1 | <1 | 8 | <1 | 0 |
| **General Disorders** | | | | | | |
| Fatigue | 40 | 6 | <1 | 28 | 1 | <1 |
| Febrile neutropenia (drug-related) | 6 | 5 | <1 | 2 | 1 | 0 |
| **Immune System Disorder** | | | | | | |
| Allergic Reaction/ Hypersensitivity | 5 | 0 | 0 | 3 | <1 | 0 |
| **Musculoskeletal & Connective Tissue Disorders** | | | | | | |
| Myalgia | 33 | 4 | 0 | 33 | 3 | <1 |
| Arthralgia | 24 | 3 | 0 | 22 | 2 | <1 |
| **Peripheral Nervous System Disorders** | | | | | | |
| Neuropathy-sensory | 64 | 5 | <1 | 58 | 3 | 0 |
| Neuropathy-motor | 15 | 2 | <1 | 10 | <1 | 0 |
| **Respiratory Disorders** | | | | | | |
| Dyspnea | 9 | 2 | <1 | 3 | 0 | 0 |
| Hypoxia | <1 | 0 | 0 | <1 | <1 | 0 |
| **Skin & Subcutaneous Tissue Disorders** | | | | | | |
| Alopecia | 90 | 14 | 4 | 92 | 19 | 3 |

[a] The toxicities above are as measured by the CTC scale, Version 2.0 (Study JHQG). [b] Regardless of causality.
[c] Non-laboratory events were graded only if assessed to be possibly drug-related.
Abbreviations: N = number of patients; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

**Hematologic**
In Study JHQG, more Grade 3 and 4 hematologic toxicities were reported with gemcitabine hydrochloride plus paclitaxel than paclitaxel alone. There was an increased incidence of red blood cell and/or whole blood transfusions (10% *versus* 4%), erythropoietin use (8% *versus* 3.5%), and granulocyte colony-stimulating factor use (7.6% *versus* 1.2%) in the gemcitabine hydrochloride plus paclitaxel arm than in the paclitaxel alone arm, respectively. There was a higher incidence of febrile neutropenia in the gemcitabine hydrochloride plus paclitaxel arm than in the paclitaxel alone arm (5% *versus* 1%; $p<0.05$); however, there was not an increased incidence of Grade 3 and 4 infections (<1%) or hemorrhagic events (0%). Of the patients experiencing febrile neutropenia (5%) in the gemcitabine hydrochloride plus paclitaxel arm, the majority of patients required hospitalization and dose adjustments.

**Hepatic**
Grade 3 and 4 liver enzyme elevation (ALT/AST) occurred in 8% of the patients treated with gemcitabine hydrochloride plus paclitaxel, and in 2% of the patients treated with paclitaxel alone.

**Neurotoxicity**
Eleven patients in the gemcitabine hydrochloride plus paclitaxel arm and 4 patients in the paclitaxel alone arm discontinued study due to neuropathy. In the gemcitabine hydrochloride plus paclitaxel arm, the majority of patients with neuropathy reported the onset after Cycle 2, while in the paclitaxel alone arm, most patients with neuropathy reported the onset after Cycle 4. Nearly half of the patients on each treatment arm reported Grade 3 or 4 neuropathy that lasted for more than one cycle.

**Pulmonary**
Grade 3 and 4 pulmonary toxicity characterized as dyspnea or hypoxia (2% *versus* <1%), were more common in the gemcitabine hydrochloride plus paclitaxel arm compared with the paclitaxel alone arm. Dyspnea was reported as worsening at the time of disease progression in patients who had this symptom reported at the time of study entry. All patients who reported dyspnea as Grade 3 or 4 toxicity and most who reported it as a serious adverse event had metastatic disease in the lungs and/or pleural effusion. No patients discontinued from the study because of grade 3 or 4 dyspnea.

**Other Grade 3 or 4 Toxicities**
Grade 3 and 4 non-laboratory toxicities were more common in the gemcitabine hydrochloride plus paclitaxel arm.

The incidence of Grade 3 and 4 fatigue was 6% in the gemcitabine hydrochloride plus paclitaxel arm and 2% in the paclitaxel alone arm ($p<0.05$); however, there were no discontinuations due to Grade 3 or 4 fatigue. Grade 3 and 4 fatigue was reported for only one cycle in most patients on both treatment arms and was not associated with anemia.

Alopecia was common and was noted in both treatment arms (18% Grade 3/4 alopecia in the gemcitabine hydrochloride plus paclitaxel arm, and 22% Grade 3/4 alopecia in the paclitaxel alone arm).

## Post-Market Adverse Drug Reactions

### Cardiovascular
Heart failure has been reported. Arrhythmias, predominantly supraventricular in nature, have been reported signaling awareness of the possibility of cardiovascular events.

### Genito-Urinary System
Hemolytic uremic syndrome (HUS) has been reported in patients receiving gemcitabine hydrochloride. In these patients, renal failure may not be reversible even with discontinuation of therapy, and dialysis may be required (see WARNINGS and PRECAUTIONS: Renal section).

### Hepatobiliary
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. These increases were not all transient, mild or non-progressive (see WARNINGS AND PRECAUTIONS, Hepatic).

### Injury, Poisoning, and Procedural Complications
Radiation toxicity and radiation recall reactions have been reported (see DRUG INTERACTIONS).

### Nervous System
Posterior reversible encephalopathy syndrome has been reported (see WARNINGS and PRECAUTIONS: Nervous system section).

### Respiratory
Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis, or adult respiratory distress syndrome (ARDS)) have been reported in association with gemcitabine hydrochloride therapy some of which may be attributed to capillary leak syndrome (see WARNINGS AND PRECAUTIONS: Vascular section, Post-Market Adverse Drug Reactions: Vascular section).

### Skin and Appendages
Severe skin reactions, including desquamation and bullous skin eruptions, have been reported .

### Vascular
Peripheral vasculitis, gangrene, and capillary leak syndrome have been reported (see WARNINGS AND PRECAUTIONS: Vascular section).

Several cases reported from clinical trials and post-market surveillance describe incidents of capillary leak syndrome (some fatal), which sometimes recurred upon subsequent gemcitabine injection.

There is some evidence to support a causal relationship between gemcitabine and CLS due to temporal relationship, recurrence upon subsequent gemcitabine injection, and biological plausibility.

## DRUG INTERACTIONS

### Overview
The radiosensitizing effects of gemcitabine hydrochloride are reviewed below.

### Drug-Drug Interactions
Interactions with other drugs have not been established.

### Drug-Food Interactions
Interactions with food have not been established.

### Drug-Herb Interactions
Interactions with herbal products have not been established.

### Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

### Drug-Radiation Interactions
Concurrent radiotherapy (given together or ≤ 7 days apart): Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine hydrochloride, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitizing activity. In a single trial where gemcitabine hydrochloride at a dose of 1 000 $mg/m^2$ was administered once weekly for up to six (6) consecutive weeks concurrently with therapeutic thoracic radiation to patients with NSCLC, significant toxicity was observed in the form of severe, and potentially life-threatening mucositis, especially esophagitis and pneumonitis, particularly in patients receiving large volumes of radiotherapy [median treatment volumes 4 795 $cm^3$]. The optimum regimen for safe administration of gemcitabine hydrochloride with therapeutic doses of radiation has not yet been determined.

Radiation injury has been reported on targeted tissues (e.g. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine hydrochloride. In addition, radiation recall has been seen with non-concurrent use.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- Gemcitabine Injection is for intravenous use only.
- Gemcitabine Injection should be administered by healthcare professionals experienced in the administration of chemotherapeutic drugs.
- Patients should be monitored prior to each dose for granulocyte and platelet counts.
- Periodic physical examination and checks of renal and hepatic function should be made to detect non-hematologic toxicity.
- Dosage escalation or reduction should be based upon the degree of toxicities experienced by the patient.

### Treatment Discontinuation

Acute shortness of breath in association with gemcitabine hydrochloride administration may occur. Bronchodilators, corticosteroids and/or oxygen produce symptomatic relief. Some reports of parenchymal lung toxicity were consistent with drug-induced pneumonitis in association with the use of gemcitabine hydrochloride (see ADVERSE REACTIONS). The mechanism of this toxicity is not known. Patients suspected of experiencing drug-induced pneumonitis should be discontinued and not be re-challenged with the drug.

### Recommended Dose

Dosage – Pancreatic Cancer

Gemcitabine Injection should be used by IV infusion at a dose of 1 000 mg/m$^2$ over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by one week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.

For dose adjustment guidelines, see Dosage Adjustment, Dose Modifications for Pancreatic Cancer, Non-Small Cell Lung Cancer and TCC of the Bladder Patients below.

Dosage – Non-Small Cell Lung Cancer

Single-agent Gemcitabine Injection should be administered by IV infusion at a dose of 1 000 mg/m$^2$ over 30 minutes once weekly for three consecutive weeks, followed by a one-week rest period. This 4-week cycle is repeated.

Gemcitabine hydrochloride has been given in combination with cisplatin on either a 4-week or a 3-week schedule. With the 4-week schedule, Gemcitabine Injection should be administered intravenously at 1 000 mg/m$^2$ over 30 minutes on Days 1, 8, and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 100 mg/m$^2$ on Day 1 after the infusion of Gemcitabine Injection. With the 3-week schedule, Gemcitabine Injection should be administered intravenously at 1 250 mg/m$^2$ over 30 minutes on Days 1 and 8 of each 21-day cycle. Cisplatin at

a dose of 100 mg/m$^2$ should be administered intravenously after the infusion of Gemcitabine Injection on Day 1. See cisplatin prescribing information for administration and hydration guidelines.

For dose adjustment guidelines, see Dosage Adjustment, Dose Modifications for Pancreatic Cancer, Non-Small Cell Lung Cancer and TCC of the Bladder Patients below.

Dosage – TCC of the Bladder

Gemcitabine Injection should be administered by IV infusion at a dose of 1 000 mg/m$^2$ over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Cisplatin should be administered intravenously at 70 mg/m$^2$ on Day 1 of each 28-day cycle. This 4-week schedule is then repeated. See cisplatin prescribing information for administration and hydration guidelines. A clinical trial showed more myelosuppression when cisplatin was used in doses of 100 mg/m$^2$.

For dose adjustment guidelines, seeDosage Adjustment, Dose Modifications for Pancreatic Cancer, Non-Small Cell Lung Cancer and TCC of the Bladder Patients below.

Dosage – Breast Cancer

Gemcitabine hydrochloride has been given in combination with paclitaxel. It is recommended to administer paclitaxel (175 mg/m$^2$) on Day 1 over approximately 3 hours as an intravenous infusion, followed by Gemcitabine Injection (1 250 mg/m$^2$) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Patients should have an absolute granulocyte count ≥1500 x 10$^6$/L and a platelet count ≥100 000 x 10$^6$/L prior to each cycle. See paclitaxel prescribing information for administration guidelines.

For dose adjustment guidelines, see Dosage Adjustment, Dose Modifications for Breast Cancer Patients below.

## Dosage Adjustment

Dose Modifications for Pancreatic Cancer, Non-Small Cell Lung Cancer, and TCC of the Bladder Patients

Patients receiving Gemcitabine Injection should be monitored prior to each dose for granulocyte and platelet counts and, if necessary, the dose of Gemcitabine Injection may be either reduced or withheld in the presence of hematological toxicity according to the guidelines in Table 5.

**Table 5:** Dose Adjustments Based on Granulocyte and Platelet Counts

| **Absolute Granulocyte Count (x 10$^6$/L)** | | **Platelet Count (x10$^6$/L)** | **% of Full Dose** |
|---|---|---|---|
| >1000 | and | >100 000 | 100 |
| 500-1000 | or | 50 000-100 000 | 75 |
| <500 | or | <50 000 | hold |

Periodic physical examination and checks of renal and hepatic function should be made to detect non-hematologic toxicity. Doses may be reduced or withheld based upon the level of toxicity.

Doses should be reduced or withheld until toxicity has resolved in the opinion of the physician.

Dose Modifications for Breast Cancer Patients
Patients should be monitored prior to each dose with a complete blood count, including differential counts.

Gemcitabine Injection dosage adjustments for hematological toxicity are based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Gemcitabine Injection dosage should be modified according to the guidelines in Table 6.

**Table 6:** Day 8 Dosage Reduction Guidelines for Gemcitabine Hydrochloride in Combination with Paclitaxel.

| **Absolute Granulocyte Count (x $10^6$/L)** | | **Platelet Count (x$10^6$/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 |

Periodic physical examination and checks of renal and hepatic function should be made to detect non-hematologic toxicity. Doses may be reduced or withheld based upon the level of toxicity.

Doses should be reduced or withheld until toxicity has resolved in the opinion of the physician.

For severe (Grade 3 or 4) non-hematological toxicity, therapy should be held or decreased by 50% depending on the judgement of the treating physician.

**Administration**
Gemcitabine hydrochloride is well tolerated during the infusion, with only a few cases of injection site reaction reported. There have been no reports of injection site necrosis. Gemcitabine hydrochloride also does not appear to act as a vesicant in a case of extravasation. Gemcitabine Injection may be administered on an outpatient basis.

As with other toxic compounds, caution should be exercised in handling and preparing solutions with gemcitabine hydrochloride. The use of gloves is recommended. If the solution of gemcitabine hydrochloride contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water or rinse the mucosa with copious amounts of water.

The appropriate amount of drug may be administered as prepared or further diluted with 0.9% sodium chloride injection or 5% glucose injection to concentrations as low as 0.1 mg/mL.

Sterile isotonic saline (0.9% sodium chloride injection) without added preservatives should be used as a diluent.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.

See STORAGE AND STABILITY for more details.

## OVERDOSAGE

There is no known antidote for overdoses of gemcitabine hydrochloride. Myelosuppression, and paresthesia were the principal toxicities seen when a single dose as high as 5 700 mg/m$^2$ was administered by IV infusion over 30 minutes every 2 weeks to several patients in a Phase I study. In the event of a suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

**For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.**

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Gemcitabine hydrochloride is a cell-cycle dependent oncolytic agent of the "antimetabolite" class. It is a deoxycytidine analog (difluoro-deoxycytidine; dFdC) that is metabolized intracellularly to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effects of gemcitabine are exerted through dFdCDP-assisted incorporation of dFdCTP into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis.

### Pharmacokinetics

Gemcitabine disposition was studied in five patients who received a single 1 000 mg/m$^2$/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. Gemcitabine plasma protein binding is negligible.

The pharmacokinetics of gemcitabine were examined in 353 patients, about 2/3 men, with various solid tumours. 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 (70-285 minutes). The total gemcitabine dose varied from 500 to 3 600 mg/m$^2$.

Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single- and multiple-dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. 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 7 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

**Table 7:** Gemcitabine Clearance and Half-Life for the "Typical" Patient

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

[a] Half-life for patients receiving a short infusion (<70 min)

Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 $L/m^2$ following infusions lasting <70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 $L/m^2$, reflecting slow equilibration of gemcitabine within the tissue compartment.

The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions. The metabolite was excreted in urine without undergoing further biotransformation and did not accumulate with weekly dosing. Its elimination is dependent on renal excretion and the metabolite could accumulate with decreased renal function.

In patients with NSCLC or bladder cancer receiving combination therapy with gemcitabine plus cisplatin, the plasma concentrations of gemcitabine and its major metabolite, dFdU, did not differ significantly from those observed in patients receiving single-agent gemcitabine.

The effects of significant renal or hepatic insufficiency on the disposition of gemcitabine have not been assessed.

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.

## STORAGE AND STABILITY

Unopened vials of Gemcitabine Injection (solution) are stable until the expiration date indicated on the package when refrigerated between 2°C and 8°C and protected from freezing.

Parenteral drugs should be inspected visually for particulate matter and discolouration, prior to administration. Dilutions prepared using 0.9% sodium chloride injection or 5% glucose injection should be used immediately or if not used immediately the solution should be used within 24 hours stored between 15°C and 30ºC. Any unused solution should be discarded.

**Special Handling Instructions**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Gemcitabine Injection (40 mg/mL) is a clear, colourless to pale yellow sterile solution available in single-use vials in the following formats: 200 mg/5 mL (5 mL vial), 1 g/25 mL (50 mL vial) and 2 g/50 mL (50 mL vial).

Each 200 mg/5 mL vial of Gemcitabine Injection contains 200 mg of gemcitabine (as the hydrochloride salt) and water. Each 1 g/25 mL vial contains 1 gram of gemcitabine (as the hydrochloride salt) and water. Each 2 g/50 mL vial of Gemcitabine Injection contains 2 grams of gemcitabine (as the hydrochloride salt) and water. Hydrochloric acid may have been added for pH adjustment.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

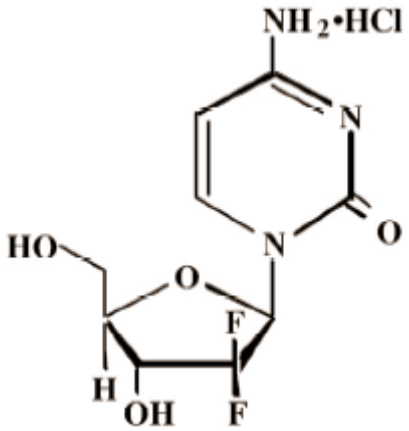
**Drug SubstanceProper Name:** gemcitabine hydrochloride

**Chemical Name:** 2'-Deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer)

**Molecular Formula:** $C_9H_{11}F_2N_3O_4 \cdot HCl$

**Molecular Mass:** 299.66 g/mol

**Structural Formula:**




**Physicochemical Properties:**

- white to off-white solid
- soluble in water
- slightly soluble in methanol
- practically insoluble in ethanol and polar organic solvents
- the pH value is between 2.0 to 3.0 in aqueous solution at 10 mg/mL and the pKa is 3.6

## CLINICAL TRIALS

**Pancreatic Cancer:** Data from two clinical trials evaluated the use of gemcitabine hydrochloride in patients with locally advanced or metastatic pancreatic cancer. The first trial compared gemcitabine hydrochloride to 5-Fluorouracil (5-FU) in patients who had received no prior chemotherapy. A second trial studied the use of gemcitabine hydrochloride in pancreatic cancer patients previously treated with 5-FU or a 5-FU-containing regimen. In both studies, the first cycle of gemcitabine hydrochloride was administered intravenously at a dose of 1 000 $mg/m^2$ 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 hydrochloride. Subsequent cycles consisted of injections once weekly for 3 consecutive weeks out of every 4 weeks.

The primary efficacy parameter in these studies was "clinical benefit response", which is a measure of clinical improvement based on analgesic consumption, pain intensity, performance status and weight change. Definitions for improvement in these variables were formulated prospectively during the design of the two 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 twenty point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least four consecutive weeks, without showing any sustained worsening in any of the other parameters. Sustained worsening was defined as four consecutive weeks with either any increase in pain intensity or analgesic consumption or a 20 point decrease in performance status occurring during the first 12 weeks of therapy.

OR

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

The first study was a multicentre (17 sites in US and Canada), prospective, single-blinded, two-arm, randomized, comparison of gemcitabine hydrochloride 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 $mg/m^2$ for 30 minutes. The results from this randomized trial are shown in Table 8. Patients treated with gemcitabine hydrochloride had statistically significant increases in clinical benefit response, survival, and time to progressive disease compared to 5-FU. The Kaplan-Meier curve for survival is shown in Figure 1.

**Table 8:** Gemcitabine Hydrochloride *Versus* 5-FU in Pancreatic Cancer

| | **Gemcitabine Hydrochloride** | **5-FU** | |
|---|---|---|---|
| Number of patients | 63 | 63 | |
| Male | 34 | 34 | |
| Female | 29 | 29 | |
| Median age | 62 years | 61 years | |
| Range | 37 to 79 | 36 to 77 | |
| Stage IV disease | 71.4% | 76.2% | |
| Baseline KPS[a] ≤70 | 69.8% | 68.3% | |
| Clinical benefit response | 23.8% (N[c] = 15) | 4.8% (N = 3) | p=0.0022 |
| Survival | | | |
| Median | 5.7 months | 4.2 months | p=0.0009 |
| 6-month probability [b] | (N=30) 46% | (N=19) 29% | |
| 9-month probability [b] | (N=14) 24% | (N=4) 5% | |
| 1-year probability [b] | (N=9) 18% | (N=2) 2% | |
| Range | 0.2 to 18.6 months | 0.4 to 15.1 + months | |
| 95% C.I. of the median | 4.7 to 6.9 months | 3.1 to 5.1 months | |
| Time to Progressive Disease | | | |
| Median | 2.3 months | 0.9 months | p=0.0002 |
| Range | 0.1 + to 9.4 months | 0.1 to 12.0 + months | |
| 95% C.I. of the median | 1.9 to 3.4 months | 0.9 to 1.1 months | |

[a] Karnofsky Performance Status
[b] Kaplan-Meier estimates
[c] N = number of patients
+ No progression at last visit; remained alive.
The p-value for clinical benefit response was calculated using the 2-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.

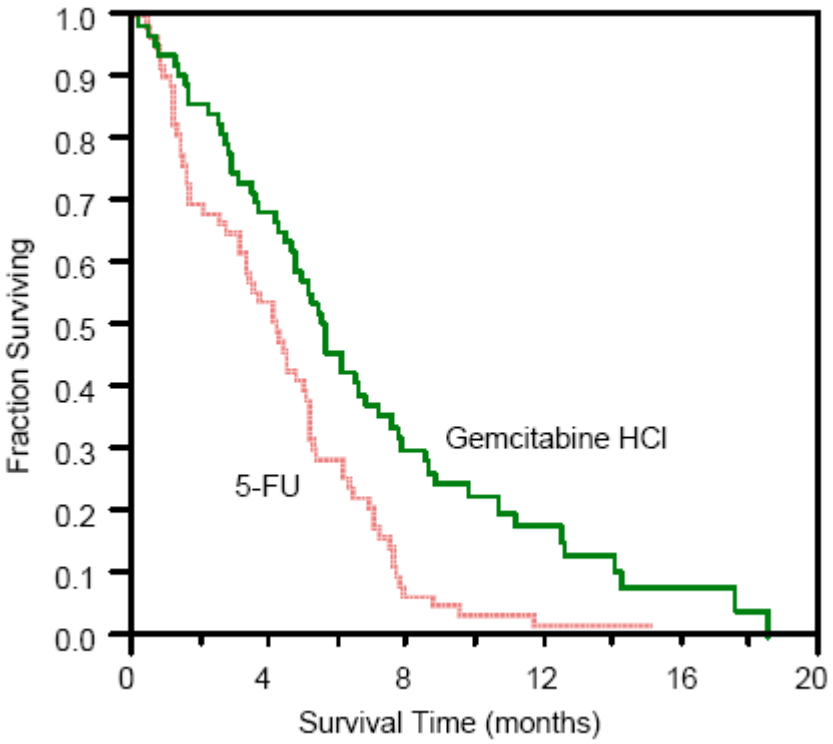



**Figure 1:** Kaplan-Meier Survival Curve – Gemcitabine Hydrochloride *versus* 5-FU in Pancreatic Cancer.

Clinical benefit response was achieved by 15 patients treated with gemcitabine hydrochloride and 3 patients treated with 5-FU. One patient on the gemcitabine hydrochloride arm showed improvement in all three primary parameters (pain intensity, analgesic consumption, and performance status). Twelve patients on the gemcitabine hydrochloride arm and two patients on the 5-FU arm showed improvement in analgesic consumption and/or pain intensity with stable performance status. Two patients on the gemcitabine hydrochloride 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.

The second trial was a multicenter (17 US and Canadian centers), open-label study of gemcitabine hydrochloride 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.

**Non-Small Cell Lung Cancer:** Data from three randomized clinical studies (806 patients) support the use of gemcitabine hydrochloride, as a single agent or in combination with cisplatin, for the treatment of patients with locally advanced or metastatic NSCLC.

**Gemcitabine Hydrochloride *Versus* Cisplatin Plus Etoposide:** Single-agent gemcitabine hydrochloride was compared to the combination regimen of cisplatin plus etoposide in previously

untreated patients with Stage IIIA, IIIB or IV NSCLC. Patients randomized to gemcitabine hydrochloride (N=72) received 1 000 mg/m$^2$ on days 1, 8, and 15 of a 28-day cycle. Patients randomized to cisplatin plus etoposide (N=75) received 100 mg/m$^2$ of cisplatin on day 1 and 100 mg/m$^2$ of etoposide intravenously on days 1, 2 and 3 of each 28-day cycle. The primary endpoint was objective tumour response rate. Single-agent gemcitabine hydrochloride was as effective as the standard combination regimen of cisplatin plus etoposide in the treatment of chemonaive NSCLC. The objective tumour response rate for gemcitabine hydrochloride was 17.9%, as compared to 15.3% for cisplatin plus etoposide, and there were no complete responses with either treatment. Median survival was estimated to be 6.6 months for gemcitabine hydrochloride patients and 7.6 months for cisplatin plus etoposide patients. The median time to progressive disease was 4.1 months in both treatment groups. Adverse events were less frequent with single-agent gemcitabine hydrochloride as compared to the combination regimen.

**Gemcitabine Hydrochloride Plus Cisplatin *Versus* Cisplatin:** This multicenter study enrolled 522 patients with inoperable Stage IIIA, IIIB or IV NSCLC who had not received prior chemotherapy. Gemcitabine hydrochloride 1 000 mg/m$^2$ was administered on days 1, 8, and 15 of a twenty-eight day cycle with cisplatin 100 mg/m$^2$ administered on day 1 of each cycle. Single-agent cisplatin 100 mg/m$^2$ was administered on day 1 of each 28-day cycle. The primary endpoint was survival.

Efficacy data are summarized in Table 9, and the Kaplan-Meier survival curve is shown in Figure 2. Median survival time on the gemcitabine hydrochloride plus cisplatin arm was 9.1 months compared to 7.6 months on the single-agent cisplatin arm (Logrank p=0.0040, two-sided). Median time to disease progression was 5.6 months on the gemcitabine hydrochloride plus cisplatin arm compared to 3.7 months on the cisplatin arm (Logrank p=0.0013, two-sided). The objective response rate on the gemcitabine hydrochloride plus cisplatin arm was 30.4% compared to 11.1% with cisplatin (Fisher's Exact p<0.0001, two-sided). No differences between treatment arms with regard to median time to tumour response and duration of response were observed.

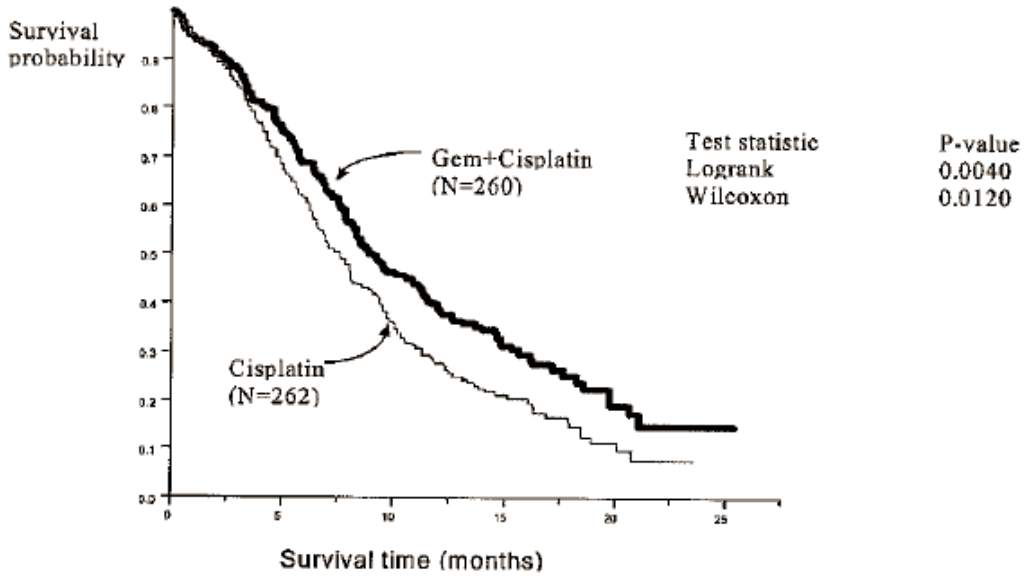



**Figure 2 :** Kaplan-Meier Survival Curves - Gemcitabine Hydrochloride plus Cisplatin *Versus* Cisplatin in Non-Small Cell Lung Cancer.

**TABLE 9:** Gemcitabine plus Cisplatin in Non-Small Cell Lung Cancer.

| | **Study JHEX** | | | **Study JHBR** | | |
|---|---|---|---|---|---|---|
| **Efficacy Measure** | **Gemcitabine plus Cisplatin (N=260)** | **Cisplatin (N=262)** | **Significance** | **Gemcitabine plus Cisplatin (N=69)** | **Cisplatin PLUS Etoposide (N=64)** | **Significance** |
| Tumour Response | 30.4% | 11.1% | Fisher's Exact Test[a] | 40.6% | 21.9% | Fisher's Exact Test |
| CR[b] | 3 (1.2%) | 1 (0.4%) | p<0.0001 | none | none | p=0.0253 |
| PR | 76 (29.2%) | 28 (10.7%) | | 28 (40.6%) | 14 (21.9%) | |
| PRNM | 1 (0.4%) | 1 (0.4%) | | none | none | |
| SD | 97 (37.3%) | 111(42.4%) | | 30 (43.5%) | 28 (43.8%) | |
| PD | 38 (14.6%) | 86 (32.8%) | | 6 (8.7%) | 14 (21.9%) | |
| Not Evaluable | 20 (7.7%) | 17 (6.5%) | | 1 (1.4%) | none | |
| Unknown | 25 (9.6%) | 18(6.9%) | | 4 (5.8%) | 8 (12.5%) | |
| Median Survival | 9.1 months | 7.6 months | Log-Rank p=0.0040 | 8.7 months | 7.2 months | |
| 6-month probability | 69% | 61% | Wilcoxon p=0.0120 | 72% | 63% | |
| 9-month probability | 50% | 42% | | 46% | 42% | |
| 1-year probability | 39% | 28% | | 30% | 24% | |
| Median Time to Progressive Disease[c] | 5.6 months | 3.7 months | Log-Rank p=0.0013 Wilcoxon p=0.0003 | 6.9 months | 4.3 months | Log-Rank p=0.0503 Wilcoxon p=0.0110 |
| Median Time to Treatment Failure[d] | 3.6 months | 2.6 months | Log-Rank p=0.0026 Wilcoxon p=0.0040 | 4.1 months | 3.1 months | Log-Rank p=0.2818 Wilcoxon p=0.0419 |
| Median Time to Tumour Response[e] | 1.9 months | 1.8 months | | 1.4 months | 1.5 months | |
| Duration of Tumour Response [f] | 6.1 months | 6.7 months | | 8.7 months | 6.5 months | |

[a] Where a statistically significant difference was observed between treatment arms, the statistical test and p-value have been noted.
[b] Abbreviations: CR, complete response; PR, partial response; PRNM, partial response non-measurable disease; SD, stable disease; PD, progressive disease,
[c] The time from randomization until the time that the patient was classified as having progressive disease.
[d] The time from randomization until the time that the patient discontinued from the study.
[e] The number of months from randomization until tumour response was observed.
[f] JHEX: the time from first objective status assessment of CR or PR to the first time of progression or death due to any cause. JHBR: for PRs, the time from randomization to the first time of progression or death due to any cause.

**Gemcitabine Hydrochloride Plus Cisplatin *Versus* Etoposide Plus Cisplatin:** A second, multicenter study in Stage IIIB or IV NSCLC randomized 135 patients to gemcitabine hydrochloride 1 250 mg/m$^2$ on days 1 and 8, and cisplatin 100 mg/m$^2$ on day 1 of a 21-day cycle or to etoposide 100 mg/m$^2$ IV on days 1,2, and 3 and cisplatin 100 mg/m$^2$ on day 1 of a 21-day cycle (Table 9). The primary endpoint was objective tumour response rate.

The objective tumour response rate for gemcitabine hydrochloride plus cisplatin was significantly higher than that for cisplatin plus etoposide, 40.6% *versus* 21.9% (Fisher's Exact p=0.0253, two- sided). Median time to disease progression for the gemcitabine hydrochloride plus cisplatin arm was 6.9 months compared to 4.3 months on the etoposide plus cisplatin arm (Logrank p=0.0338, two-sided). There was no significant difference in survival between the two treatment arms (Logrank p=0.l8, two-sided). The median survival was 8.7 months for the gemcitabine hydrochloride plus cisplatin arm *versus* 7.2 months for the etoposide plus cisplatin arm.

**Bladder Cancer [Transitional Cell Carcinoma (TCC) of the Urothelium]-**Data from a randomized, multicenter, phase III clinical trial (405 patients with Stage IV TCC of the bladder) and two phase II trials support the use of gemcitabine hydrochloride in combination with cisplatin for the first-line treatment of patients with Stage IV (locally advanced or metastatic) TCC of the bladder.

The primary objective of the randomized, phase III trial was to compare survival of patients with Stage IV (locally advanced or metastatic) TCC of the bladder treated with either gemcitabine hydrochloride plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Patients had not received any prior systemic chemotherapy. Patients were randomized to one of the following intravenous treatments:

i) Gemcitabine 1 000 mg/m$^2$ on Days 1, 8, and 15, and cisplatin 70 mg/m$^2$ on Day 2 of each 28-day cycle,

OR

ii) Methotrexate 30 mg/m$^2$ on Days 1, 15, and 22, vinblastine 3 mg/m$^2$ on Days 2, 15, and 22, doxorubicin 30 mg/m$^2$ on Day 2, and cisplatin 70 mg/m$^2$ on Day 2 of each 28-day cycle.

The secondary endpoints of this study were one-year survival probability, time to disease progression, response rates, duration of response, toxicity profile, and changes in quality of life. Patient demographics are shown in Table 10.

The Kaplan-Meier survival curve is shown in Figure 3 and efficacy data are summarized in Table 11. Median survival time on the gemcitabine hydrochloride plus cisplatin arm was 12.8 months compared to 14.8 months on the MVAC arm (Logrank p=0.55). Median time to disease progression was 7.4 months on the gemcitabine hydrochloride plus cisplatin arm compared to 7.6 months on the MVAC arm (Logrank p=0.84). The overall response rate on the gemcitabine hydrochloride plus cisplatin arm was 49.4% compared to 45.7% on the MVAC arm (Chi-square p=0.51). Median duration of response was 9.6 months on the gemcitabine hydrochloride plus cisplatin arm compared to 10.7 months on the MVAC arm. Time to treatment failure on the gemcitabine hydrochloride plus cisplatin arm was 5.8 months *vs* 4.6 months on the MVAC arm

(Logrank p=0.l39). Significantly more patients on gemcitabine hydrochloride plus cisplatin had an increase in weight over baseline compared to MVAC patients (27% *vs* 12% p=0.001).

Gemcitabine hydrochloride plus cisplatin was better tolerated than MVAC based on the indicators of tolerability discussed below and shown in Table 12. Gemcitabine hydrochloride plus cisplatin patients received a median of 6 cycles of treatment *vs* a median of 4 cycles for MVAC patients. Gemcitabine hydrochloride plus cisplatin patients experienced significantly fewer episodes of neutropenic sepsis than MVAC patients (1% *vs* 11.9%, p<0.00l). Patients on gemcitabine hydrochloride plus cisplatin experienced fewer episodes of febrile neutropenia resulting in hospitalization than did those on MVAC [9 hospital admissions (33 days) *vs* 49 hospital admissions (272 days)]. Fewer gemcitabine hydrochloride plus cisplatin patients required colony-stimulating factors than did MVAC patients (6% *vs* 20%). Gemcitabine hydrochloride plus cisplatin patients experienced less Grade 3 and 4 alopecia than did MVAC patients (11% *vs* 55%). Grade 3 and 4 nausea and vomiting occurred in approximately 20% of the patients in both treatment arms. Grade 3 and 4 mucositis occurred in 1% of gemcitabine hydrochloride plus cisplatin patients *vs* 22% of MVAC patients (p=0.001).

**Table 10:** Randomized Trial of Combination Therapy with Gemcitabine Hydrochloride plus Cisplatin *vs* MVAC in TCC of the Bladder.

| **Treatment Arm** | **Gemcitabine Hydrochloride plus Cisplatin** | **MVAC** |
|---|---|---|
| Number of patients (%) | N= 203 | N=202 |
| Male | 160 (79) | 160 (79) |
| Female | 43 (21) | 42 (21) |
| Median age, years | 63 | 63 |
| Range | 34-83 | 38-83 |
| Baseline Disease (%) | | |
| Stage IV | 203 (100) | 202 (100) |
| Tb4 only | 16 (8) | 19(9) |
| Metastaic ($M_1$) | 141(69) | 127(63) |
| Visceral | 99 (49) | 93 (46) |
| Baseline KPS [a] (%) | | |
| 60 to 80 | 90 (45) | 92 (48) |
| 90 to 100 | 109 (55) | 101 (52) |

[a] Karnofsky Performance Scale

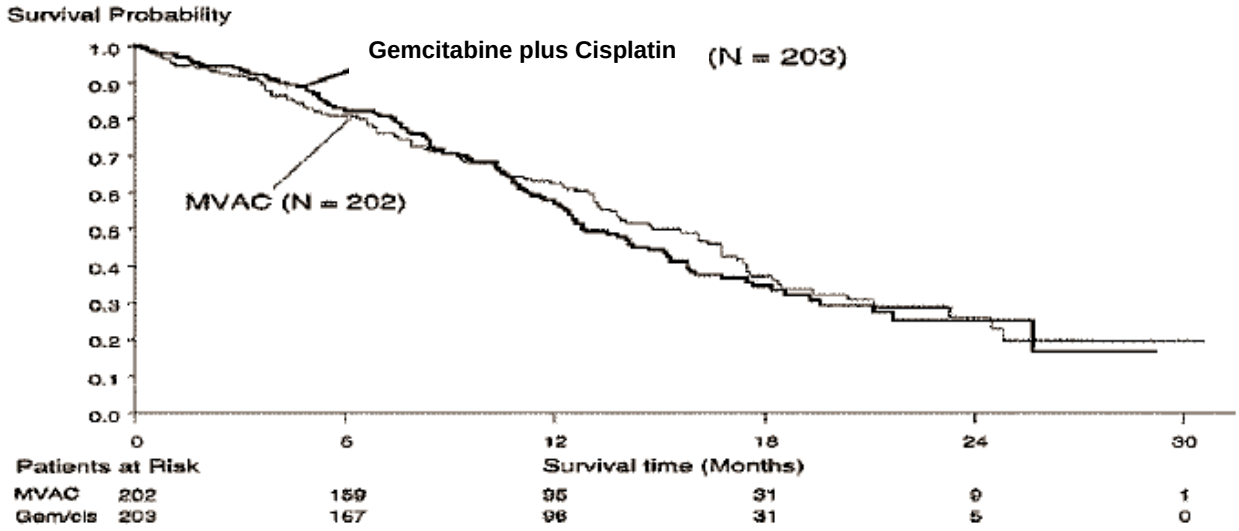



**Figure 3:** Kaplan-Meier Survival Curve in Gemcitabine Hydrochloride plus Cisplatin *versus* MVAC Bladder Cancer Study (N=405).

**Table 11:** Efficacy Data from Pivotal Randomized Trial of Combination Therapy with Gemcitabine Hydrochloride plus Cisplatin *vs* MVAC in TCC of the Bladder

| **Treatment Arm** | **Gemcitabine Hydrochloride plus Cisplatin** | **MVAC** | |
|---|---|---|---|
| Survival<br>Median, months<br>(95% C.I.) months<br>1 year survival probability (%) | N=203<br>12.8<br>12.0-15.3<br>56.9 | N=202<br>14.8<br>13.2-17.2<br>62.4 | p=0.55 |
| Time to Disease Progression<br>Median, months<br>(95% C.I.) months | <br>7.4<br>6.0-8.1 | <br>7.6<br>6.7-9.1 | p=0.84 |
| Tumour Response (%)<br>Overall | N=164<br>49.4 | N=151<br>45.7 | p=0.51[a] |
| Duration of Response,<br>Median, months | 9.6 | 10.7 | p=0.48 |
| Time to treatment Failure<br>Median, months | 5.8 | 4.6 | p=0.14 |

[a] p-value for tumour response was calculated using the 2-sided Pearson Chi-square test for difference in binomial proportions. All other p-values were calculated using the Log-rank test for difference in overall time to event.

**Table 12:** Indicators of Tolerability from the Randomized Trial of Gemcitabine Hydrochloride plus Cisplatin *versus* MVAC.

| **Treatment Arm (N)** | **Gemcitabine Hydrochloride plus Cisplatin (203)** | **MVAC (202)** | |
|---|---|---|---|
| Median cycles of therapy | 6 | 4 | |
| Total cycles of therapy | 943 | 792 | |
| Neutropenia (%) | | | |
| Grade 3 | 41 | 17 | |
| Grade 4 | 30 | 65 | |
| Neutropenic sepsis (%) | 1 | 11.9 | p<0.001 |
| Febrile neutropenia | | | |
| Hospitalizations[a] | 9 | 49 | |
| Duration of stay [b] | 33 | 272 | |
| Colony-stimulating factors (%) | 6 | 20 | |
| Alopecia (%) | | | |
| Grades 3 and 4 | 11 | 55 | |
| Mucositis (%) | | | |
| Grades 3 and 4 | 1 | 22 | p=0.001 |
| Nausea/Vomiting | | | |
| Grades 3 and 4 | 22 | 21 | |

[a] Patient admissions due to febrile neutropenia

[b] Days of hospitalization due to febrile neutropenia.

**Quality of Life (QOL):** QOL was measured using the EORTC QLQ-C30, which assessed physical and psychological functioning and symptoms related to cancer and its treatment. Both arms noted improvement in pain and emotional functioning. Fatigue worsened in the MVAC arm but did not change in the gemcitabine hydrochloride plus cisplatin arm. In all other scales, QOL was maintained in both treatment arms.

**Additional Supporting Studies:** A phase II nonrandomized trial using gemcitabine hydrochloride in combination with cisplatin in 46 patients with Stage IV (metastatic) TCC of the bladder who had not received treatment for metastatic disease supports the use of gemcitabine hydrochloride plus cisplatin as treatment for this disease. The regimen in this study was gemcitabine hydrochloride 1 000 mg/m$^2$ on Days 1, 8 and 15 and cisplatin 75 mg/m$^2$ on Day 1 of each 28-day cycle. The first 11 patients received cisplatin 100 mg/m$^2$ on Day 1; however, Grade 3/4 neutropenia (100%) and thrombocytopenia (73%) in the 11 patients resulted in a dose reduction to 75 mg/m$^2$. In this study, the response rate was 41% and the median survival was 14.3 months. A second phase II [31 patients with Stage IV (locally advanced or metastatic) TCC of the bladder] trial used the same regimen as in the randomized trial. In this study the response rate was 57% and the median survival was 12.6 months. In both these trials, overall toxicities were similar to those seen in the randomized phase III trial.

**Breast Cancer:** Data from the pivotal study, JHQG (N=529), support the use of gemcitabine hydrochloride in combination with paclitaxel for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant anthracycline-based chemotherapy. In this multicentre, open-label, randomized Phase 3 study of metastatic breast cancer patients who have received prior adjuvant/neoadjuvant chemotherapy, 267 patients

were randomly assigned to the gemcitabine hydrochloride plus paclitaxel arm and 262 patients were randomly assigned to the paclitaxel alone arm.

The study objectives were to compare overall survival, time to documented disease progression (TtDPD), progression-free survival (PFS), response rates, duration of response, and toxicities between patients treated with gemcitabine hydrochloride plus paclitaxel combination therapy and those treated with paclitaxel monotherapy.

The Kaplan-Meier plot of overall survival for randomized patients is shown in Figure 4, while the overall efficacy results of Study JHQG are summarized below and in Table 13:

- Survival analysis showed improvement in the gemcitabine hydrochloride plus paclitaxel arm compared with the paclitaxel alone arm, as demonstrated by a longer median survival (18.6 *versus* 15.8 months, with a hazard ratio of 0.817 (95% confidence interval [CI], 0.667 to 1.000, log-rank p=0.0489).

- Median time to documented progression of disease (TtDPD) was 5.4 months (95% CI 4.6 to 6.1 months) for patients on the gemcitabine hydrochloride plus paclitaxel arm and 3.5 months (95% CI 2.9 to 4.0 months) for patients on the paclitaxel alone arm.

- The gemcitabine hydrochloride plus paclitaxel arm demonstrated statistically significant improved PFS (5.3 months *versus* 3.5 months, p=0.0021), and response rate (39% *versus* 26%, p=0.0007) over the paclitaxel alone arm. There was no statistical significant difference in duration of response between treatment arms.

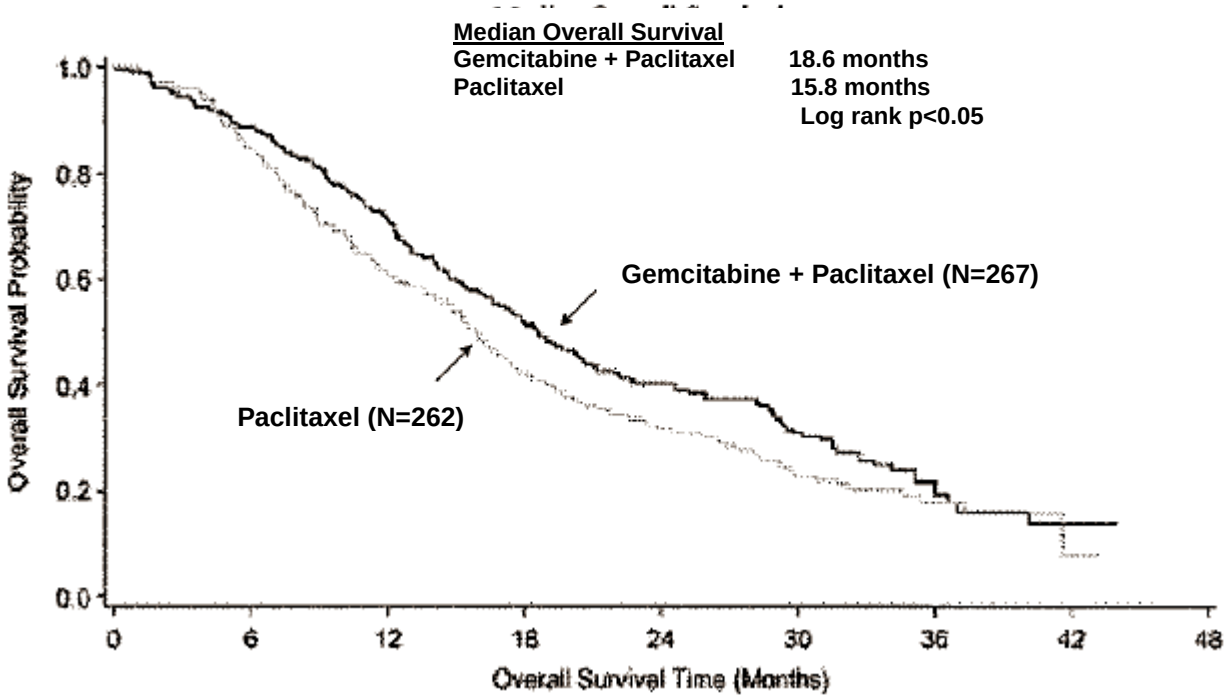



**Figure 4:** Kaplan-Meier Plot of Overall Survival in Randomized Patients, Study JHQG.

**Table 13:** Efficacy Results of Pivotal Trial Study JHQG Supporting Combination Therapy of Gemcitabine Hydrochloride plus Paclitaxel in Patients with Metastatic Breast Cancer.

| | **Study JHQG** | |
|---|---|---|
| **Efficacy Endpoint** | **Gemcitabine Hydrochloride plus Paclitaxel (N=267)** | **Paclitaxel Alone (N=262)** |
| Median Overall Survival [a] | 18.6 months | 15.8 months |
| 95% CI | 16.6 to 20.7 months | 14.4 to 17.4 months |
| log-rank test | p=0.0489 | |
| HR (95% CI); Wald test | HR: 0.817 (0.667 to 1.000); P=0.495 | |
| Median TtDPD [b] | 5.4 months | 3.5 months |
| 95% CI | 4.6 to 6.1 months | 2.9 to 4.0 months |
| log-rank test | p=0.0013 | |
| HR (95% CI); Wald test | HR: 0.734 (0.607 to 0.889); p=0.0015 | |
| Median TtDPD/PFS [c] | 5.3 months PFS | 3.5 months PFS |
| 95% CI | 4.4 to 5.9 months | 2.8 to 4.0 months |
| log-rank test | p=0.0021 | |
| HR (95% CI); Wald test | HR: 0.749 (0.621 to 0.903); p=0.0024 | |
| Response rate-investigator-assessed | 39% (105/267) | 26% (67/262) |
| 95% CI | 34% to 45% | 20% to 31% |
| number of patients with CR/PR/SD | 18 CR/87 PR/90 SD | 11 CR/56 PR/94 SD |
| z-test for normal approximation | p=0.0007 | |
| Response rate-independently reviewed [d] | 46% (90/198) | 26% (47/184) |
| 95% CI | 39% to 52 % | 19% to 32% |
| number of patients with CR/PR/SD | 9 CR/81 PR/71 SD | 2 CR/45 PR/78 SD |
| z-test for normal approximation | p=0.00005 | |

[a] The censoring rate for median overall survival was 31.6% for the gemcitabine hydrochloride plus paclitaxel arm and 25.9% for the paclitaxel alone arm.
[b] The censoring rate for TtDPD was 23% for gemcitabine hydrochloride plus paclitaxel arm and 17% for the paclitaxel alone arm.
[c] The censoring rate for PFS was 18% for gemcitabine hydrochloride plus paclitaxel arm and 14% for the paclitaxel alone arm.
[d] Overall best study response was determined by independent review for 382 patients (198 gemcitabine hydrochloride plus paclitaxel arm, 184 paclitaxel alone arm).

Abbreviations: N= number of patients; TtDPD = time to documented progression of disease; CI =confidence interval; HR = hazard ratio; PFS =progression-free survival; CR= complete response; PR = partial response; SD = stable disease.

**Other Clinical Studies**
Dose-Range Studies: When gemcitabine hydrochloride 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 hydrochloride 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/m$^2$. The incidence and severity of these events were dose-related. Other Phase 1 studies using a twice-weekly schedule reached MTDs of only 65 mg/m$^2$ (30-minute infusion) and 150 mg/m$^2$ (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/m$^2$ at or above a 270-minute infusion time. The half-life of gemcitabine is influenced by the length of the infusion (see ACTION AND CLINICAL PHARMACOLOGY) and the toxicity appears to be increased if gemcitabine hydrochloride is administered more frequently than once weekly or with infusions longer than 60 minutes (see WARNINGS AND PRECAUTIONS).

## DETAILED PHARMACOLOGY

**Cellular Metabolism and Mechanisms of Action**
Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and, under certain conditions, blocking the progression of cells through the G1/S-phase boundary. *In vitro* the cytotoxic action of gemcitabine is both concentration-dependent and time-dependent.

Gemcitabine (difluoro-deoxy-cytidine; dFdC) is metabolized intracellularly by nucleotide kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleotides. The cytotoxic action of gemcitabine appears to be due to inhibition of DNA synthesis by two actions of dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase which is uniquely responsible for catalyzing the reactions that generate the deoxynucleotide triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleotides in general, and especially in that of dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA. Likewise, a small amount of gemcitabine may also be incorporated into RNA. Thus, the reduction in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA. DNA polymerase epsilon is essentially unable to remove gemcitabine and repair the growing DNA strands. After gemcitabine is incorporated into DNA, one additional nucleotide is added to the growing DNA strands. After this addition there is essentially a complete inhibition in further DNA synthesis (masked chain termination). After incorporation into DNA, gemcitabine appears to induce the programmed cellular death process known as apoptosis.

**Anti-tumour Activity**
***In vivo:*** In animal tumour models, the anti-tumour activity of gemcitabine is schedule-dependent. When administered daily gemcitabine causes significant animal lethality with very little anti-tumour activity. However, when an every third or fourth day dosing schedule is used gemcitabine can be given at nonlethal doses that have an excellent anti-tumour activity against a broad range of murine tumours. For example, at nontoxic doses gemcitabine inhibits by 95-100% the growth

of the following subcutaneously growing murine tumours: X5563 plasma cell myeloma, 6C3HED lymphosarcoma, CA-755 mammary adenocarcinoma and M5 ovarian carcinoma. Gemcitabine inhibits the growth of subcutaneously growing B16 melanoma in the range of 60-80%. Gemcitabine produces significant increases in the lifespan of mice bearing the leukemia models P388 and L1210 in the range of 50-200%. Gemcitabine also inhibits the growth of P 1534J and Friend Leukæmia in the order of 90%.

Gemcitabine has anti-tumour activity against a broad spectrum of human tumours grown as xenografts in immunologically deficient mice. As with murine tumours, optimum anti-tumour activity is seen when gemcitabine is given on a staggered dosing schedule. Several studies have shown that gemcitabine, at nontoxic doses, inhibits by 90-100% the growth of the following human carcinoma xenografts: non-small cell lung, mammary, colon, gastric, pancreatic, ovarian and head and neck.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*, and no effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. When tested against the CALU-6 human lung adenocarcinoma xenograft, gemcitabine plus cisplatin produced 80% tumour regression and 98% tumour growth inhibition, without toxicity, and was more effective than gemcitabine alone at preventing regrowth of this tumour. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

## TOXICOLOGY

### Repeat Dose Toxicity Studies

In repeat dose studies of up to 6 months in duration in mice and dogs, the principal finding was hematopoietic suppression. These effects were related to the cytotoxic properties of the drug and were reversible when treatment was withdrawn. The degree of the effect was schedule and dose-dependent.

### Carcinogenicity, Mutagenicity, and Fertility Studies

Chromosomal damage, including chromatid breaks, has been produced by gemcitabine in *in vitro* studies. Gemcitabine caused a reversible, dose and schedule dependent hypospermatogenesis in male mice. Although animal studies have shown an effect of gemcitabine on male fertility, no effect has been seen on female fertility. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of gemcitabine. 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 vivo* 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 $mg/m^2$ basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice fertility was not affected but, maternal toxicities were observed at 1.5 mg/kg/day IV (about 1/200 the

human dose on a mg/m$^2$ basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day IV (about 1/1 300 the human dose on a mg/m$^2$ basis).

The results of the toxicology studies involving gemcitabine are presented in **Tables 14** to **17**.

**Table 14:** Results Of Acute Toxicity Studies With Gemcitabine Hydrochloride.

| Species, Strain | No/Sex /Group; Age | Doses (mg/kg/day) | Route of Administration | Duration of Observation | Parameters Evaluated | Observations |
|---|---|---|---|---|---|---|
| Mouse, ICR | 5/sex; 4-5 wk | 0, 500 | IV[a] | 2 wk | Mortality, clin.obs., body wt., gross pathology | Poor grooming; ↓body wt. gain; leg weakness & clonic convulsion in control & treated mice; MLD>500 mg/kg |
| Rat, Fischer 344 | 5F; 8-9 wk | 0, 16, 33, 70, 160 | IV[a] | 2 wk | Mortality, clin.obs., body wt., gross pathology | Poor grooming, leg weakness; hypoactivity, diarrhea, ataxia, chromorhinorrhea, swollen face, chromodacryorrhea, emaciation, tremors, clonic convulsions, dark urine, pale eyes; MLD=64 mg/kg |
| Mouse, ICR | 5/sex; 4-5 wk | 0, 500 | IV[c] | 2 wk | Mortality, clin.obs., body wt., gross pathology | Leg weakness, hair loss; MLD>500 mg/kg. |
| Rat, Fischer | 5F; 8-9 wk | 0, 16, 33, 45, 70, 90, 160 | IV[c] | 2 wk | Mortality, clin.obs., body wt., gross pathology | Poor grooming, leg weakness; hypoactivity, soft stool, diarrhea, excessive hair loss, emaciation, chromodacryorrhea, ptosis, pale eyes; MLD=236 mg/kg. |
| Dog, Beagle | 1/sex; 8-10 mo | 3, 12, 18, 24 | IV[c] | 2 wk | Mortality, clin.obs., body wt., food consumption, hematology, clinical chem. | soft or mucoid stool, reversible neutropenia; MLD>24 mg/kg. |

[a] m-cresol/phenol diluent
[b] MLD = Median Lethal Dose
[c] Saline Diluent

**Table 15:** Results of Subchronic and Chronic Toxicity Studies With Gemcitabine Hydrochloride

| Species, Strain | No/Sex/ Group; Age | Doses (mg/kg) | Route of Administration | Duration of Treat-ment | Parameters Evaluated | Observations |
|---|---|---|---|---|---|---|
| **Subchronic Studies** | | | | | | |
| Dog, Beagle | 4/sex; 7-9 mo. | 0, 0.1 (daily) 1.5 (2x wkly) | IV | 3 months | Survival; clin.obs.; physical & ophthalmic exams; body wt.; food consumption; hematol.; clinical chem.; urinalysis; organ wt.; pathology. | Abnormal stools; reversible mild to moderate ↓ leucocytes & platelets in 1.5 mg/kg reversible minimal ↓erythrocyte count in 0.1 mg/kg group; hypoplasia of thymus & testes & ↓postmitomyeloid pool in bone marrow in 1.5 mg/kg group. |
| Mouse, $B6C3F_1$ | 15/sex; 5-6 wk | 0, 1 (daily) 5, 20 (2X weekly) 40 (once weekly) | IP | 3 months | Survival; clin.obs.; body wt.; hematology; clinical chem.; organ wt.; pathology. | ↓hemoglobin, PVC, erythrocyte & leukocyte counts in 1 mg/kg group; ↑spleen & ↓ testes wt.; splenic erythropoiesis & spermatogenesis. |
| **Chronic Studies** | | | | | | |
| Mouse, CD-1 | 30/sex; 5-6 wk | | IP | 6 months; 2 month recovery | Survival; clin.obs.; body wt.; hematology; clinical chem.; organ wt.; pathology. | Mortality (3), ↓body wt.&wt. gain; reversible ↓ erythrocyte & lymphocyte counts, reversible ↑BUN & ↓total protein, ↓testes wt. ↑spleen wt., splenic erythropoiesis, lymphoid hypoplasia in 0.5 mg/kg group; hypospermatogenesis in all treated males partially reversible. |
| Mouse, CD-1 | 15/sex; 5-6 wk | | IV | 6 months; 6 weeks recovery | Survival; clin.obs.; body wt.; food consumption; hematology; clinical chem.; organ wt.; pathology. | Slight ↓ body wt.; reversible ↓ erythrocyte count, ↓testes wt.; ↑spleen wt.; hypospermatogenesis in 0.3 mg/kg group; spleen & testes changes partially reversible. |
| Dog, Beagle | 3-4/sex; 7-9 months | | IV | 6 months; 6 weeks recovery | Survival; clin.obs.; body wt.; food consumption; physical & ophthalmic exams; ECG; hematology.; clinical chem.; urinalysis; organ wt.; pathology. | Reversible slight ↓ erythrocyte count in 0.2 mg/kg group; slight ↓ lymphocyte & neutrophil counts in 0.2 & 0.3 mg/kg groups. |

**Table 16:** Results of Reproduction Studies With Gemcitabine Hydrochloride.

| Species, Strain | No./Sex/ Group; Age | Doses (mg/kg) | Route of Administration | Duration of Treatment | Parameters Evaluated | Observations |
|---|---|---|---|---|---|---|
| Mouse, $B6C3F_1$ | 20 M; 5 wk | 0, 0.05,0.5 (daily) 3.5, 10 (weekly) | IP | 10 wk prior to mating, throughout mating | Survival; clin.obs.; body wt.; food cons. ;mating performance; fertility; resorptions; fetal parameters; testes wt. & histopath. | ↓fertility, implantation (0.5 mg/kg daily)↓ testicular wt.; Hypospermatogenesis (0.5 mg/kg/day & 3.5 & 10 mg/kg/day) |
| Mouse, CD-1 | 25 F; 9 wk | 0, 0.05, 0.25, 1.5 (daily) | IV | 2 wk prior to mating; through Gestion Day 6 | Survival; clin.obs.; body wt.; food cons. ; mating performance; fertility; resorptions; fetal parameters;hematology; organ wt. | ↓fetal viability; ↓fetal wt.; ↑%fetal runts; slight ↑ PCV; hemoglobin,MCV,MCH; ↑spleen wt. (1.5 mg/kg/day). |
| Mouse, CD-1 | 25 F (teratology) 20 F (Postnatal);adult, virgin | 0, 0.05, 0.1, 0.25,1.5 (daily) | IV | Gestion Days 6-15 | Survival; clin.obs.; body wt.; food consumption; reproduction ($F_0$ & $F_1$); fetal parameters; progeny measurements ($F_0$ & $F_1$ ); $F_0$ preweaning & $F_1$ postweaning behaviour; hematology $F_0$ pathology ($F_0$ & $F_1$ generations). | ↑vaginal discharge & abortions; ↓body wt.,food cons.;(1.5 mg/kg/day). ↑spleen wt. (0.05,0.25 & 1.5 mg/kg/day). ↓liver wt.; ↑thymus wt.; ↓fetal wt.; ↓fetal malformations (1.5 mg/kg/day) ↓ liveborn progeny, ↓ progeny survival; ↓progeny wt. (1.5 mg/kg/day). ↓relative ovary wt. in all F1groups. ↓startle reactivity in F1 males (0.05 & 1.5 mg/kg/day groups). ↑MCV, MCH (0.25 & 1.5 mg/kg/day). |
| Mouse, CD-1 | 25 F; adult, virgin | 0, 0.05, 0.1, 0.25, 1.5 (daily) | IV | Gestion Day 15-Postpartum Day 20 | Survival; clin.obs.; body wt.; food consumption; organ wts. ($F_0$ & $F_1$); reproduction & progeny measurements ($F_0$ & $F_1$ ); preweaning & postweaning behaviour; hematology ($F_0$) ; pathology ($F_0$ & $F_1$). | ↓fetal viability, ↓fetal wt.; ↑ malformations & deviations (0.1mg/kg/day), ↓erythrocytes, hemoglobin, PCV (0.1 mg/kg/day). |
| Rabbit, New Zealand White | 20 F; mated adult | 0, 0.0015, 0.005, 0.1 (daily) | IV | Gestion Days 6-18 | Survival; clin.obs.; body wt.; food consumption; hematology; fetal viability, fetal wt., morphology. | ↓fetal viability, ↓fetal wt.; ↑ malformations & deviations (0.1 mg/kg/day) ; ↓erythrocytes, hemoglobin, PCV (0.1 mg/kg/day). |

**Table 17:** Results of Mutagenecity Studies With Gemcitabine Hydrochloride.

| **Type of Study** | **Species, Cells** | **Route of Administration** | **Doses/Concentrations** | **Results** |
|---|---|---|---|---|
| Ames | *Salmonella typhimurium, Escherichia coli* | Not Applicable | 125 to 5000 mcg/plate | Negative nonactivated & activated |
| Unscheduled DNA | Adult rat hepatocites | Not Applicable | 0.5 to 1000 mcg/mL | Negative |
| Forward mutation at thymidine kinase locus | L5178Y TK+/- mouse lymphoma | Not Applicable | 0.001 to 0.06 mcg/mL | Positive non- activated & with metabolic activation |
| Sister chromatid exchange in bone marrow | Chinese hamster | Intraperitoneal | 3.125 to 50 mg/kg | Negative |
| Chromosome aberration | Chinese hamster ovary | Not Applicable | 0.005 to 0.03 mcg/mL, 0.04 to 0.1mcg/mL | Negative nonactivated; with metabolic activation |
| Micronucleus | Mouse, bone marrow | Intravenous | 0, 0.1875, 0.375, 0.75 mg/kg | Positive |

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**PART III: CONSUMER INFORMATION**

**[Pr] Gemcitabine Injection**
Concentrate Sterile Solution for Injection
Gemcitabine (as Gemcitabine Hydrochloride)
Solution: 40 mg of gemcitabine per mL

**This leaflet is part III of a three-part "Product Monograph" published when Gemcitabine Injection was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Gemcitabine Injection. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for**:
Gemcitabine Injection is an approved chemotherapy for treatment of:

- Non-small cell lung cancer (NSCLC), alone or in combination with another medication
- Pancreatic cancer
- Bladder cancer, in combination with another medication
- Breast cancer, in combination with another medication

**What it does:**
Gemcitabine Injection is a chemotherapy that works through disrupting the cells ability to divide or grow. Chemotherapies are active in both healthy and cancer cells. However, cancer cells are known to divide or grow at a faster rate than most healthy cells making chemotherapies such as Gemcitabine Injection effective in the treatment of various cancers. While the time it takes to see if Gemcitabine Injection shrinks your cancer varies from person to person, your doctor will ask you if you are feeling better and will perform regularly scheduled examinations and x-rays to determine if Gemcitabine Injection has been effective.

**When it should not be used:**
Do not take Gemcitabine Injection if you have had an allergic or sensitivity reaction to this drug or any of its ingredients (see **What the important nonmedicinal ingredients are** section of this leaflet).

**What the medicinal ingredient is:**
Gemcitabine hydrochloride

**What the important nonmedicinal ingredients are:**
Water for injection and hydrochloric acid may have been added for pH adjustment.

**What dosage forms it comes in:**
Gemcitabine Injection (40 mg/mL) concentrate sterile solution is available in the following formats: 200 mg/5 mL (5 mL vial), 1 g/25 mL (50 mL vial) and 2 g/50 mL (50 mL vial).

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- **Gemcitabine Injection should only be prescribed by physicians experienced with delivery of chemotherapy.**
- **Gemcitabine Injection is intended for intravenous use only.**
- **Gemcitabine Injection infusion times longer than 60 minutes and given more often than once per week are known to increase negative side effects.**
- **As with other chemotherapies, there is a risk of side effects, sometimes severe, with Gemcitabine Injection therapy.**
- **Gemcitabine Injection routinely leads to a fall in blood counts which, if severe can lead to an increased risk of infection and bleeding.**
- **Gemcitabine Hydrochloride has been associated with a type of pneumonia that can be quite severe in less than 1 in 1 000 patients and less severe in less than 1 in 100 patients.**

**BEFORE you receive Gemcitabine Injection talk to your doctor if:**

- You have had an allergic reaction to any chemotherapy or have been treated with any chemotherapy in the past.
- You are pregnant, plan on becoming pregnant, or are currently breast feeding.
- You have liver or kidney problems, or a bone marrow disorder.

## INTERACTIONS WITH THIS MEDICATION

Gemcitabine Injection is known to increase your body's sensitivity to radiation therapy.

It is very important to tell your doctor about any medications you may be taking, including over the counter drugs, such as Aspirin® (acetylsalicylic acid), vitamins, and other pain relievers. Be sure to check with your doctor before taking any medications on your own.

## PROPER USE OF THIS MEDICATION

**Usual Dose:**
Your doctor will develop a Gemcitabine Injection treatment plan based on your needs. You are encouraged to discuss your treatment plan with your doctor. There are many points your doctor will consider when selecting the appropriate treatment plan for you. Your doctor may recommend skipping a dose based upon your response to Gemcitabine Hydrochloride for Injection.

**Overdose:**
Gemcitabine Injection will be given under the supervision of a qualified physician. Any overdose should be managed by a qualified physician experienced in the use of anticancer agents.

In case of drug overdose, contact a health care practitioner, hospital emergency or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Contact your healthcare professional immediately for further instructions.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In clinical studies of gemcitabine hydrochloride, side effects were generally manageable. Side effects significant enough to cause your treatment to be stopped occurred in about 10% of all patients. Less than 1% of patients stopped therapy due to any one side effect. Most side effects were reversible and can be managed by either a delay in your treatment, a reduction of the dose of chemotherapy or both. Therefore, it is important for you to know about common side effects and for you to communicate any suspected side effects to your doctor.

You should discuss possible side effects with your doctor before beginning Gemcitabine Injection therapy and at any time you think you may be experiencing a side effect. For a list of possible side effects see the **Call Your Doctor or Nurse If You Experience** section and **Serious Side Effects** table below.

In clinical studies of gemcitabine hydrochloride, the most common reason for dosage adjustments was low blood counts. About two thirds of patients had low blood counts. In about one fourth of patients, decreases in blood counts were severe. For more information speak with your doctor and see section below on **Low Blood Counts**.

Shortness of breath may develop or worsen during treatment due to disease progression or in rare cases, due to a direct effect of the drug. If this occurs, patients should inform their treating doctor immediately of the developing or worsening of shortness of breath.

Nausea and vomiting were the most common side effects in clinical studies of gemcitabine hydrochloride. About two thirds of patients experienced nausea and vomiting, which were usually mild to moderate. Other common side effects included fever, swelling, rash, and flu-like symptoms.

In rare cases, gemcitabine hydrochloride may affect your liver, especially if you have liver metastases (spreading of cancer) or medical history of hepatitis (inflammation of the liver), alcoholism or liver cirrhosis (liver disease). Follow your doctor's instructions on having periodic blood work to check your liver.

In rare cases, gemcitabine hydrochloride may affect your kidney, especially if your kidney function is not normal. Follow your doctor's instructions on having periodic blood work to check your kidneys.

**Low Blood Counts:**
Chemotherapy drugs often affect the blood cells, which means that temporary changes in their counts may occur. These effects may be more common in patients older than 65 and in women. Blood tests will be done before each dose of Gemcitabine Hydrochloride for Injection to monitor your blood counts.

If your doctor notices changes in your blood counts, follow their advice, which may include:

**White Blood Count:**
- if your white blood count becomes low, you may have trouble fighting infections.
- stay out of crowds and away from people with colds or other illnesses.
- call your doctor if you develop a temperature over 38°C.
- ensure regular mouth care to reduce chance of infection.

**Red Blood Count:**
- if your red blood count becomes low, you may feel tired or weak. If it becomes too low, your doctor may recommend a red blood cell transfusion.
- rest as much as you need to.
- try to eat a well-balanced diet.

**Platelet Count:**
- if your platelet count becomes low, your blood may not clot as fast as usual, and bleeding or bruising may occur. Sometimes a blood transfusion is given if platelet counts drop very low.
- try to avoid getting cuts, bumps, or bruises (for example avoid contact sport and using a razor).
- since acetylsalicylic acid can affect your platelets, you should avoid taking acetylsalicylic acid while you are receiving chemotherapy, unless your doctor advises otherwise.

**Call Your Doctor or Nurse If You Experience:**
- any unusual bruising or bleeding.
- any pain around an infusion site.
- a sore mouth or throat.
- prolonged or uncomfortable swelling.
- severe diarrhea, meaning three or more watery bowel movements per day, lasting more than 24 hours.
- severe constipation for three days that has not been relieved by laxatives.
- numbness or tingling in your hands or feet.
- vomiting for more than 24 hours after your treatment.
- any changes in your skin, especially rash or potential allergic skin reactions.
- headache with confusion, and/or seizures (fits), and/or changes in vision.
- see also **Serious Side Effects** table below.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom/effect | | Talk with your doctor or nurse | |
|---|---|---|---|
| | | Only if severe | In all cases |
| Very Common | Diarrhea | | ✓ |
| | Swelling | | ✓ |
| | Vomiting | ✓ | |
| Common | Body temperature over 38°C or shaking chills | | ✓ |
| | Fatigue | ✓ | |
| Uncommon | Shortness of breath | | ✓ |
| Very rare | Skin reactions including blistering | | ✓ |
| Very rare | Headache with confusion, and/or seizures (fits), and/or changes in vision | | ✓ |

*This is not a complete list of side effects. For any unexpected effects while taking Gemcitabine Injection, contact your doctor or nurse.*

## HOW TO STORE IT

Gemcitabine Injection should be refrigerated between 2°C and 8°C. Do not freeze.

Dilutions prepared using 0.9% sodium chloride injection or 5% glucose injection should be used immediately or if not used immediately the solution should be used within 24 hours stored between 15 ºC and 30ºC. Any unused solution should be discarded.

Handling and storage of Gemcitabine Injection is restricted to qualified healthcare professionals. Keep out of reach of children.

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

1. Report online at www.healthcanada.gc.ca/medeffect
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
   - Fax toll-free to 1-866-678-6789, or
   - Mail to: Canada Vigilance Program
     Health Canada
     Postal Locator 0701E
     Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062
or
by written request at:
145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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