carboplatin study, dose reductions occurred with 10.4 % of Gemcitabine injections and 1.8 % of carboplatin injections on the combination arm, versus 3.8 % on the carboplatin alone arm. On the combination arm, 13.7 % of Gemcitabine doses were omitted and 0.2 % of carboplatin doses were omitted, compared to 0 % of carboplatin doses on the carboplatin alone arm. There were no differences in discontinuations due to adverse events between arms (10.9 % versus 9.8 %, respectively).
Blood transfusions included both packed red blood cells and whole blood. In addition to Blood transfusions included both packed red blood cells and whole blood. In addition to blood product transfusions, myelosuppression was also managed with hematopoetic agents. These agents were administered more frequently with combination therapy than with monotherapy (granulocyte growth factors: 23.6 % and 10.1 %, respectively; erythropoetic agents: 7.3 % and 3.9 %, respectively).
The following are the clinically relevant adverse events, regardless of causality, that occurred in >1 % and <10 % (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse events (Gemcitabine plus carboplatin versus carboplatin): AST or ALT elevation (0 versus 1.2 %), dyspnea (3.4 % versus 2.9 %), febrile neutropenia (1.1 % versus 0), hemorrhagic event (2.3 % versus 1.1 %), hypersensitivity reaction (2.3 % versus 2.9 %), motor neuropathy (1.1 % versus 0.6 %), and rash/desquamation (0.6 % versus 0).
No differences in the incidence of laboratory and non laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.
Post marketing experience: The following adverse events have been identified during post approval use of Gemcitabine. These events have occurred after Gemcitabine single agent use and Gemcitabine in combination with other cytotoxic agents. Decisions to include these events are based on the seriousness of the event, frequency of reporting, or potential causal connection to Gemcitabine.
Cardiovascular - Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemcitabine. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.
Vascular Disorders - Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.
Skin - Cellulitis and non serious injection site reactions in the absence of extravasation have been rarely reported. Severe skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.
Hepatic - Increased liver function tests including elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs.
Pulmonary - Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of Gemcitabine administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemcitabine dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.
Renal – Hemolytic Uremic Syndrome (HUS) and/or renal failure have been reported following one or more doses of Gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.
Injury, Poisoning, and Procedural Complications - Radiation recall reactions have been reported.

OVERDOSAGE(S)

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

DOSAGE & ADMINISTRATION

GEMWEL™ is for intravenous use only. Gemcitabine for Injection may be administered on an outpatient basis.
Ovarian Cancer: GEMWEL™ should be administered intravenously at a dose of 1000 mg/m^2 over 30 minutes on days 1 and 8 of each 21 day cycle. Carboplatin AUC 4 should be administered intravenously on day 1 after Gemcitabine for Injection administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.
Dose modifications: Gemcitabine for Injection dosage adjustments for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on day 8 of therapy. If marrow suppression is detected, Gemcitabine for Injection dosage should be modified according to guidelines in table.
Table: Day 8 dosage reduction guidelines for Gemcitabine for Injection in combination with Carboplatin

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
=1500	and/or	=100,000	100
1000-1499		75,000-99,999	50
<1000		<75,000	Hold

In general, for severe (Grade 3 or 4) non hematological toxicity, except nausea/vomiting, therapy with Gemcitabine for Injection should be held or decreased by 50 % depending on the judgment of the treating physician.
Dose adjustment for Gemcitabine for Injection in combination with carboplatin for subsequent cycles is based upon observed toxicity. The dose of Gemcitabine for Injection in subsequent cycles should be reduced to 800 mg/m^2 on days 1 and 8 in case of any of the following hematologic toxicities:

Absolute granulocyte count <500 x 10^6/L for more than 5 days
Absolute granulocyte count <100 x 10^6/L for more than 3 days
Febrile neutropenia
Platelets <25,000 x 10^6/L
Cycle delay of more than one week due to toxicity
If any of the above toxicities recur after the initial dose reduction, for the subsequent cycle, Gemcitabine for Injection should be given on day 1 only at 800 mg/m^2.
Breast Cancer: GEMWEL™ should be administered intravenously at a dose of 1250 mg/m^2 over 30 minutes on days 1 and 8 of each 21 day cycle.
Paclitaxel should be administered at 175 mg/m^2 on day 1 as a 3 hour intravenous infusion before Gemcitabine for Injection administration. Patients should be monitored prior to each dose with a complete blood count, including differential counts. Patients should have an absolute granulocyte count ≥1500 x 10^6/L and a platelet count ≥100,000 x 10^6/L prior to each cycle.
Dose modifications: Gemcitabine for Injection dosage adjustments for hematological toxicity is based on the granulocyte and platelet counts taken on day 8 of therapy. If marrow suppression is detected, Gemcitabine for Injection dosage should be modified according to the guidelines in table.
Table: Day 8 dosage reduction guidelines for Gemcitabine for Injection in combination with Paclitaxel

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
=1200	and/or	<75,000	100
1000-1199		50,000-75,000	75
700-999		=50,000	50
<700		<50,000	Hold

In general, for severe (Grade 3 or 4) non hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine for Injection should be held or decreased by 50 % depending on the judgment of the treating physician.

Non Small Cell Lung Cancer: Two schedules have been investigated and the optimum schedule has not been determined. With the 4 week schedule, GEMWEL™ should be administered intravenously at 1000 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 for Injection. With the 3 week schedule, Gemcitabine for Injection should be administered intravenously at 1250 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 for Injection on day 1.
Dose modifications: Dosage adjustments for hematologic toxicity may be required for Gemcitabine for Injection and for cisplatin. Gemcitabine for Injection dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemcitabine for Injection should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet counts. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in Table 3. For cisplatin dosage adjustment, see manufacturer's prescribing information.
In general, for severe (Grade 3 or 4) non hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine for Injection plus cisplatin should be held or decreased by 50 % depending on the judgment of the treating physician. During combination therapy with cisplatin, serum creatinine, serum potassium, serum calcium, and serum magnesium should be carefully monitored (Grade 3/4 serum creatinine toxicity for Gemcitabine for Injection plus cisplatin was 5 % versus 2 % for cisplatin alone).

Pancreatic Cancer: Gemcitabine for Injection should be administered by intravenous infusion at a dose of 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.
Dose modifications: Dosage adjustment is based upon the degree of hematologic toxicity experienced by the patient. Clearance in women and the elderly is reduced and women were somewhat less able to progress to subsequent cycles. Patients receiving Gemcitabine for Injection should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to the guidelines in table.
Table: Dosage reduction guidelines

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
=1000	and/or	=100,000	100
500-999		50,000-99,999	75
<500		<50,000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine for Injection should be administered with caution in patients with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.
Patients treated with Gemcitabine for Injection who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25 %, provided that the absolute

granulocyte count (AGC) and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively and if non hematologic toxicity has not been greater than WHO Grade 1. If patients tolerate the subsequent course of Gemcitabine for Injection at the increased dose, the dose for the next cycle can be further increased by 20 %, provided again that the AGC and platelet nadirs exceed 1500 x 10^6/L and 100,000 x 10^6/L, respectively, and that non-hematologic toxicity has not been greater than WHO Grade 1.

Preparation for intravenous infusion administration
The recommended diluent for reconstitution of GEMWEL™ is 0.9 % sodium chloride injection without preservatives. Due to solubility considerations, the maximum To reconstitute, add 5 ml of 0.9 % sodium chloride injection to the 200 mg vial or 25 ml of 0.9 % sodium chloride injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml which includes accounting for the displacement volume of the lyophilized powder (0.26 ml for the 200 mg vial or 1.3 ml for the 1 g vial). The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9 % sodium chloride injection to concentrations as low as 0.1 mg/ml.
Reconstituted GEMWEL™ is a clear, colorless to light straw colored solution. After reconstitution with 0.9 % sodium chloride injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.
When prepared as directed, GEMWEL™ solutions are to be used immediately or within 24 hours if stored at 15-25°C. Discard unused portion. Solutions of reconstituted GEMWEL™ should not be refrigerated, as crystallization may occur.
The compatibility of GEMWEL™ with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

STORAGE

Store below 30°C. Do not Refrigerate.

Note : The reconstituted solution should be used immediately or within 24 hours if stored at 15-25°C. Refer the package insert for detailed information.

PRESENTATION

GEMWEL™ is presented in USP type I flint glass vials in 2 strength's, 200 mg and 1 g.

HANDLING AND DISPOSAL

Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.
Caution should be exercised in handling and preparing GEMWEL™ solutions. The use of gloves is recommended. If GEMWEL™ solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Although acute dermal irritation has not been observed in animal studies, 2 of 3 rabbits exhibited drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption. Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.

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0700DGL

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

GEMCITABINE FOR INJECTION USP

GEMWEL™

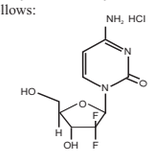
Lyophilized
Cytotoxic Agent
FOR I.V INFUSION ONLY
Rx only

WARNING

Patients on GEMWEL™ therapy should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents.
Toxicity may increases with infusion times >60 minutes or dosing more frequently than once weekly with GEMWEL™.
During therapy with GEMWEL™ it is advisable to monitor for myelosuppression, which can be dose limiting.
Discontinue GEMWEL™ immediately in case of the occurrence of severe pulmonary toxicity.
Renal function should be monitored prior to initiation of therapy and periodically thereafter. GEMWEL™ should be used with caution in patients with renal impairment. Reports suggest the occurrence of some fatal cases of hemolytic uremic syndrome (HUS) and/or renal failure. Discontinue GEMWEL™ for in the event of HUS or severe renal toxicity.
Monitor hepatic function prior to initiation of GEMWEL™ therapy and impairment. Serious hepatotoxicity, including liver failure and death may occur. Discontinue GEMWEL™ in case of severe hepatic toxicity.
GEMWEL™ can cause fetal harm. It is advisable to inform women of child bearing age on GEMWEL™ therapy of the potential risk to the fetus.
GEMWEL™ may cause severe and life threatening toxicity.

DESCRIPTION

Gemcitabine HCl is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2´- deoxy-2´, 2´- difluorocytidine monohydrochloride (β isomer).
The structural formula is as follows:



The empirical formula for Gemcitabine HCl is $C_9H_{11}F_2N_3O_4$.HCl. It has a molecular weight of 299.66.
Gemcitabine HCl is a white to off white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

COMPOSITION

Each vial of GEMWEL™ 200 mg contains:

Gemcitabine Hydrochloride USP eq. to Gemcitabine	200 mg
Mannitol IP	200 mg
Sodium acetate IP	12.5 mg

Hydrochloric acid IP and/or Sodium Hydroxide IP used to adjust the pH.

Each vial of GEMWEL™ 1g contains:

Gemcitabine Hydrochloride USP eq. to Gemcitabine	1 g
Mannitol IP	1 g
Sodium acetate IP	62.5 mg

Hydrochloric acid IP and/or Sodium Hydroxide IP used to adjust the pH.

CLINICAL PHARMACOLOGY & MECHANISM OF ACTION

Chemically Gemcitabine is a nucleoside analog in which the hydrogen atoms on the 2' carbons of deoxycytidine are replaced by fluorine atoms. Gemcitabine exhibits cell phase specificity, primarily kills cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides.
The cytotoxic effect of Gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.
Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP.
Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of Gemcitabine triphosphate into DNA (self-potentiation).
After the Gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the

Gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, Gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

PHARMACOKINETICS & PHARMACODYNAMIC

Pharmacodynamics

Reports suggest that Gemcitabine demonstrates dose dependent synergistic activity with Cisplatin in vitro. However no effect of Cisplatin on Gemcitabine triphosphate accumulation or DNA double strand breaks was observed. In vivo reports indicate that Gemcitabine shows activity in combination with Cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine is thought to be synergistic with Cisplatin in the Lewis lung murine xenograft. Sequential exposure to Gemcitabine 4 hours before Cisplatin therapy may produce the greatest interaction.

Pharmacokinetics

Absorption and Distribution

The pharmacokinetics report of Gemcitabine examined in 353 patients, with various solid tumors indicate that the pharmacokinetic parameters were derived using data from patients treated for varying durations of therapy given weekly with periodic rest weeks and using both short infusions (< 70 minutes) and long infusions (70 to 285 minutes). The total Gemcitabine for Injection dose varied from 500 to 3600 mg/m². The volume of distribution was increased with infusion length. Volume of distribution of Gemcitabine was 50 L/m² following infusions lasting < 70 minutes. For long infusions, the volume of distribution rose to 370 L/m². In general the pharmacokinetics of Gemcitabine is thought to be linear and may be described by a 2 compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies show that the volume of distribution of Gemcitabine may be significantly influenced by the duration of infusion and gender. Plasma protein binding of Gemcitabine is negligible. Gemcitabine is majorly administered by the IV route, since it is extensively metabolized by the gastrointestinal tract.

Metabolism

Reports from studies on Gemcitabine disposition in 5 patients who received a single 1000 mg/m²/30 minute infusion of radiolabeled drug indicate that within one (1) week, 92 % to 98 % of the dose was recovered, almost entirely in the urine. Gemcitabine (< 10 %) and the inactive uracil metabolite, 2´-deoxy-2´, 2´-difluorouridine (dFdU), accounted for 99 % of the excreted dose. The metabolite dFdU is also found in plasma. The active metabolite, Gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half life of the terminal phase for Gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

Excretion

Clearance of Gemcitabine may be affected by age and gender. The lower clearance may be seen in women and the elderly resulting in higher concentrations of Gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion results in changes in half-life and plasma concentration. Table 1 shows plasma clearance and half-life of Gemcitabine following short infusions for typical patients by age and gender.

Gemcitabine clearance and half life for "typical" patients

Age	Clearance Man (L/hr/M²)	Clearance Women (L/hr/M²)	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 range from 42 to 94 minutes and the value for long infusions is seen to vary from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

INDICATION(S)

Ovarian Cancer - Gemcitabine in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum based therapy.

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

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

Pancreatic Cancer - Gemcitabine is indicated as the first line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine is also indicated for patients previously treated with 5-FU.

CONTRAINDICATION(S)

Gemcitabine is contraindicated in patients with prior known hypersensitivity to the drug.

WARNING(S)

Caution - Prolongation of the infusion time beyond 60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Hematology - Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, anemia and myelosuppression is usually the

dose limiting toxicity. Patients should be monitored for myelosuppression during therapy.

Pulmonary - Pulmonary toxicity has been reported with the use of Gemcitabine. In cases of severe lung toxicity, Gemcitabine therapy should be discontinued immediately and appropriate supportive care measures instituted.

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

Hepatic - Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Pregnancy - Pregnancy Category D.

Gemcitabine can cause fetal harm when administered to a pregnant woman. Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m² basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on mg/m² basis). Embryotoxicity may be characterized by decreased fetal viability, reduced live litter sizes and developmental delays. However there are no well controlled studies of Gemcitabine in pregnant women. If Gemcitabine is used during pregnancy, or if the patient becomes pregnant while taking Gemcitabine, the patient should be apprised of the potential hazard to the fetus.

PRECAUTION(S)

General - Patients receiving GEMWEL™ should be monitored closely by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are reversible and may not result in discontinuation, although doses may need to be withheld or reduced. There is a greater tendency in women, especially older women, not to proceed to the next cycle.

Laboratory Tests - Patients receiving GEMWEL™ should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count. Suspension or modification of therapy should be considered when marrow suppression is detected. Laboratory evaluation of renal and hepatic function should be performed prior to initiation of therapy and periodically thereafter.

Carcinogenesis, Mutagenesis, Impairment of Fertility - Long term animal studies to evaluate the carcinogenic potential of Gemcitabine have not been conducted. Gemcitabine induces forward mutations in vitro in a mouse lymphoma (L5178Y) assay and was reported to be clastogenic in an in vivo mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, in vivo sister chromatid exchange, in vitro chromosomal aberration assays and did not cause unscheduled DNA synthesis in vitro. Intra peritoneal Gemcitabine doses of 0.5 mg/kg/day (about 1/700 the human dose on mg/m² basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day IV (about 1/200 the human dose on a mg/m² basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day IV (about 1/1300 the human dose on a mg/m² basis).

Pregnancy - Category D.

Nursing Mothers - It is not known whether Gemcitabine or its metabolites are excreted in human milk but since most anti-cancer drugs are excreted in human milk and because of the potential for serious adverse reactions from Gemcitabine in nursing infants, the mother should be warned and a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the potential risk to the infant.

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

Gender - Gemcitabine clearance is affected by gender. In the single agent safety database (N=979 patients), there is no evidence that unusual dose adjustments may be necessary in women. In general, in single agent studies of Gemcitabine, adverse reaction rates were similar in men and women, but women, especially older women, were more likely not to proceed to a subsequent cycle and to experience Grade 3/4 neutropenia and thrombocytopenia.

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

Patients with Renal or Hepatic Impairment - Gemcitabine should be used with caution in patients with preexisting renal impairment or hepatic insufficiency as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. Administration of Gemcitabine in patients with concurrent liver metastases or a preexisting medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

Drug Interactions - No specific drug interaction studies have been conducted. However information is available on pharmacokinetics and pharmacodynamics of Gemcitabine in combination with Cisplatin, Paclitaxel, or Carboplatin.

Radiation Therapy - A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and non concurrent use of Gemcitabine. Non concurrent (given >7 days apart) data analysis does not indicate enhanced toxicity

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

ADVERSE REACTION(S)

Gemcitabine has been used in a wide variety of malignancies, both as a single agent and in combination with other cytotoxic drugs. Information available from controlled studies conducted worldwide may be as follows:

Single agent use: Myelosuppression is the principal dose limiting toxicity with Gemcitabine therapy.

Hematologic - In studies in pancreatic cancer myelosuppression is the dose limiting toxicity with Gemcitabine, but <1 % of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19 % of patients. The incidence of sepsis was less than 1 %. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16 % of patients; less than 1 % of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity.

Gastrointestinal - Nausea and vomiting were commonly reported (69 %) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15 % of patients. Diarrhea was reported by 19 % of patients and stomatitis by 11 % of patients.

Hepatic - In clinical trials, Gemcitabine was associated with transient elevations of one or both serum transaminases in approximately 70 % of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemcitabine or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Renal - In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25 %) receiving Gemcitabine in clinical trials. Four patients developed HUS on Gemcitabine therapy, 2 immediately posttherapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

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

Rash - Rash was reported in 30 % of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13 % of patients.

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

Edema - Edema (13 %), peripheral edema (20 %) and generalized edema (<1 %) were reported. Less than 1 % of patients discontinued due to edema.

Flu like Symptoms - "Flu syndrome" was reported for 19 % of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating and malaise were reported infrequently. Less than 1 % of patients discontinued due to flu like symptoms.

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

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

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

Extravasation - Injection site related events were reported for 4 % of patients. There were no reports of injection site necrosis. Gemcitabine is not a vesicant.

Allergic - Bronchospasm was reported for less than 2 % of patients. Anaphylactoid reaction has been reported rarely. Gemcitabine should not be administered to patients with a known hypersensitivity to this drug.

Cardiovascular - During clinical trials, 2 % of patients discontinued therapy with Gemcitabine due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia and hypertension. Many of these patients had a prior history of cardiovascular disease.

Combination use in non small cell lung cancer: In the Gemcitabine plus cisplatin versus cisplatin study, dose adjustments occurred with 35 % of Gemcitabine injections and 17 % of cisplatin injections on the combination arm, versus 6 % on the cisplatin only arm. Dose adjustments were required in greater than 90 % of patients on the combination,

versus 16 % on cisplatin. Study discontinuations for possibly drug related adverse events occurred in 15 % of patients on the combination arm and 8 % of patients on the cisplatin arm. With a median of 4 cycles of Gemcitabine plus cisplatin treatment, 94 of 262 patients (36 %) experienced a total of 149 hospitalizations due to possibly treatment related adverse events. With a median of 2 cycles of cisplatin treatment, 61 of 260 patients (23 %) experienced 78 hospitalizations due to possibly treatment related adverse events.

In the Gemcitabine plus cisplatin versus etoposide plus cisplatin study, dose adjustments occurred with 20 % of Gemcitabine injections and 16 % of cisplatin injections in the Gemcitabine plus cisplatin arm compared with 20 % of etoposide injections and 15 % of cisplatin injections in the etoposide plus cisplatin arm. With a median of 5 cycles of Gemcitabine plus cisplatin treatment, 15 of 69 patients (22 %) experienced 15 hospitalizations due to possibly treatment related adverse events. With a median of 4 cycles of etoposide plus cisplatin treatment, 18 of 66 patients (27 %) experienced 22 hospitalizations due to possibly treatment related adverse events. In patients who completed more than one cycle, dose adjustments were reported in 81 % of the Gemcitabine plus cisplatin patients, compared with 68 % on the etoposide plus cisplatin arm. Study discontinuations for possibly drug related adverse events occurred in 14 % of patients on the Gemcitabine plus cisplatin arm and in 8 % of patients on the etoposide plus cisplatin arm. The incidence of myelosuppression was increased in frequency with Gemcitabine plus cisplatin treatment (~90 %) compared to that with the Gemcitabine monotherapy (~60 %). With combination therapy Gemcitabine dosage adjustments for hematologic toxicity were required more often while cisplatin dose adjustments were less frequently required.

To comprehend the safety data from the Gemcitabine plus cisplatin versus cisplatin study in non small cell lung cancer; the NCI Common Toxicity Criteria (CTC) was used. The two drug combination was more myelosuppressive with 4 (1.5 %) possibly treatment related deaths, including 3 resulting from myelosuppression with infection and one case of renal failure associated with pancytopenia and infection. No deaths due to treatment were reported on the cisplatin arm. Nine cases of febrile neutropenia were reported on the combination therapy arm compared to 2 on the cisplatin arm.

More patients required RBC and platelet transfusions on the Gemcitabine plus cisplatin arm.

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

Nausea and vomiting despite the use of antiemetics occurred slightly more often with Gemcitabine plus cisplatin therapy (78 %) than with cisplatin alone (71 %). In studies with single agent Gemcitabine, a lower incidence of nausea and vomiting (58 % to 69 %) was reported. Renal function abnormalities, hypomagnesemia, neuromotor, neurocortical and neurocerebellar toxicity occurred more often with Gemcitabine plus cisplatin than with cisplatin monotherapy. Neurohearing toxicity was similar on both arms.

Cardiac dysrrhythmias of Grade 3 or greater were reported in 7 (3 %) patients treated with Gemcitabine plus cisplatin compared to one (<1 %) Grade 3 dysrrhythmia reported with cisplatin therapy. Hypomagnesemia and hypokalemia were associated with one Grade 4 arrhythmia on the Gemcitabine plus cisplatin combination arm.

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

Combination use in breast cancer: In the Gemcitabine plus paclitaxel versus paclitaxel study, dose reductions occurred with 8 % of Gemcitabine injections and 5 % of paclitaxel injections on the combination arm, versus 2 % on the paclitaxel arm. On the combination arm, 7 % of Gemcitabine doses were omitted and <1 % of paclitaxel doses were omitted, compared to <1 % of paclitaxel doses on the paclitaxel arm. A total of 18 patients (7 %) on the Gemcitabine plus paclitaxel arm and 12 (5 %) on the paclitaxel arm discontinued the study because of adverse events. There were two deaths on study or within 30 days after study drug discontinuation that were possibly drug related, one on each arm.

The safety data occurrences of ≥10 % (all grades) from the Gemcitabine plus paclitaxel versus paclitaxel study in breast cancer being clinically relevant adverse events that occurred in >1 % and <10 % (all grades) of patients on either arm. In parentheses are the incidences of Grade 3 and 4 adverse events (Gemcitabine plus paclitaxel versus paclitaxel): febrile neutropenia (5.0 % versus 1.2 %), infection (0.8 % versus 0.8 %), dyspnea (1.9 % versus 0) and allergic reaction/hypersensitivity (0 versus 0.8 %). No differences in the incidence of laboratory and non laboratory events were observed in patients 65 years or older, as compared to patients younger than 65.

Combination use in ovarian cancer: In the Gemcitabine plus carboplatin versus