Composition : Cytogem injection : Each vial contains Gemcitabine 1 gm as Gemcitabine Hydrochloride USP lyophilized powder for injection.

Cytogem-200 injection : Each vial contains Gemcitabine USP 200 mg as Gemcitabine Hydrochloride lyophilized powder for injection.

Mechanism of Action : Gemcitabine (dFdC) is metabolised intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. 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 catalysing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by dFdCDP causes a reduction in the concentrations of deoxynucleosides in general, and especially in that of dCTP. Secondly, 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 (self-potentiation). 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 then appears to induce the programmed cellular death process known as apoptosis.

Pharmacokinetic Properties : Peak plasma concentrations (obtained within 5 minutes of the end of the infusion): 3.2 to 45.5 µg/ml. **Volume of distribution of the central compartment:** 12.4 l/m^2 for women and 17.5 l/m^2 for men (inter-individual variability was 91.9%). Volume of distribution of the peripheral compartment: 47.4 l/m^2. The volume of the peripheral compartment was not sensitive to gender. **Plasma protein binding :** Negligible. **Systemic clearance :** Ranged from 29.2 l/hr/m^2 to 92.2 l/hr/m^2 depending on gender and age (inter-individual variability was 52.2%). Clearance for women is approximately 25% lower than the values for men. Although rapid, clearance for both men and women appears to decrease with age. For the recommended Gemcitabine dose of 1,000 mg/m^2 given as a 30 minute infusion, lower clearance values for women and men should not necessitate a decrease in the Gemcitabine dose. **Urinary excretion :** Less than 10% is excreted as unchanged drug. **Renal clearance :** 2 to 7 l/hr/m^2. **Half-life :** Ranged from 42 to 94 minutes depending on age and gender. For the recommended dosing schedule, Gemcitabine elimination should be virtually complete within 5 to 11 hours of the start of the infusion. Gemcitabine does not accumulate when administered once weekly. **Metabolism :** Gemcitabine is rapidly metabolised by cytidine deaminase in the liver, kidney, blood, and other tissues. Intracellular metabolism of Gemcitabine produces the Gemcitabine mono, di, and triphosphates (dFdCMP, dFdCDP. and dFdCTP), of which dFdCDP and dFdCTP are considered active. These intracellular metabolites have not been detected in plasma or urine. The primary metabolite, 2'- deoxy-2', 2'-difluorouridine (dFdU), is not active and is found in plasma and urine. **dFdCTP Kinetics :** This metabolite can be found in peripheral blood mononuclear cells and the information below refers to these cells. **Half-life of terminal elimination :** 0.7-12 hours. Intracellular concentrations increase in proportion to Gemcitabine doses of 35-350 mg/m^2/30 min, which give steady-state concentrations of 0.4-5 µg/ml. At Gemcitabine plasma concentrations above 5 µg/ml, dFdCTP levels do not increase, suggesting that the formation is saturable in these cells. Parent plasma concentrations following a dose of 1,000 mg/m^2/30 min are greater than 5 µg.ml for approximately 30 minutes after the end of the infusion, and greater than 0.4 µg.ml for an additional hour. **dFdU Kinetics :** Peak plasma concentrations (3-15 minutes after end of 30 minute infusion, 1,000 mg/m^2): 28-52 µg/ml **Trough concentration following once weekly dosing :** 0.07-1.12 µg/ml with no apparent accumulation. **Triphasic plasma concentration versus time curve, mean half-life of terminal phase :** 65 hours (range 33-84 hours). **Formation of dFdU from parent compound:** 91%-98%. **Mean volume of distribution of central compartment :** 18 l/m^2 (range 11-22 l/m^2). **Mean steady-state volume of distribution (Vss) :** 150 l/m^2 (range 96-228 l/m^2).**Tissue distribution :** Extensive. **Mean apparent clearance :** 2.5 l/hr/m^2 (range 1-4 l/hr/m^2). **Urinary excretion :** All.

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

Pancreatic Cancer : Gemcitabine is indicated for the treatment of adult patients with locally advanced or metastatic

adenocarcinoma of the pancreas. Gemcitabine is indicated for patients with 5-FU refractory pancreatic cancer.

Bladder Cancer : Gemcitabine is indicated for treatment of advanced bladder cancer (muscle invasive Stage IV tumors with or without metastases) in combination with Cisplatin therapy.

Breast Cancer : Gemcitabine in combination with Paclitaxel, is indicated for the treatment of patients with metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contra-indicated.

Ovarian Cancer : Gemcitabine in combination with Carboplatin, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma who have relapsed following platinum-based therapy.

Dosage & Administration : Gemcitabine is for intravenous use only.

Non-Small Cell Lung Cancer : (Single-agent Use): Adults - the recommended dose of Gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for three weeks, followed by a one-week rest period. This four-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Non-Small Cell Lung Cancer : (Combination Use) : Adults- Gemcitabine, in combination with Cisplatin has been investigated using two dosing regimens. One regimen used a three-week schedule and the over used a four-week schedule. The three-week schedule used Gemcitabine 1250 mg/m^2, given by 30-minute intravenous infusion, on days 1 and 8 of each 21-day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. The four-week schedule used Gemcitabine 1000 mg/m^2, given by 30-minute intravenous infusion, on days 1,8, and 15 of each 28-day cycle. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient .

Pancreatic Cancer : Adults- the recommended dose of Gemcitabine is 1000 mg/m^2, given by 30-minute intravenous infusion. This should be repeated once weekly for up to 7 weeks followed by a week of rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder Cancer : (Single agent use): Adults- the recommended dose of Gemcitabine is 1250 mg/m^2, given by 30-minute intravenous infusion. The dose should be given on days 1,8 and 15 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Bladder Cancer : (Combination use): Adults- the recommended dose for Gemcitabine is 1000 mg/m^2, given by 30-minute infusion, The dose should be given on days 1,8 and 15 of each 28-day cycle in combination with Cisplatin. Cisplatin is given at a recommended dose of 70 mg/m^2 on day 1 following Gemcitabine or day 2 of each 28-day cycle. This 4-week cycle is then repeated. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. A clinical trial showed more myelosuppression when Cisplatin was used in doses of 100 mg/m^2.

Breast Cancer : (Combination Use): Adults- Gemcitabine in combination with Paclitaxel is recommended using Paclitaxel (175 mg/m^2) administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by Gemcitabine (1250 mg/m^2) as a 30-minute intravenous infusion on Days 1 and 8 of each 21-day cycle. Dose reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient. Patients should have an absolute granulocyte count of at least 1,500 (x106/L) prior to initiation of Gemcitabine + Paclitaxel combination.

Ovarian Cancer : (Combination use): Adults- Gemcitabine in combination with Carboplatin is recommended using Gemcitabine 1000 mg/m^2 administered on days 1 and 8 of each 21-day cycle as a 30-minute intravenous infusion. After Gemcitabine, Carboplatin should be given on day 1 consistent with target AUC of 4.0 mg/mL/min. Dosage reduction with each cycle or within a cycle may be applied based upon the amount of toxicity experienced by the patient.

Monitoring, Dose Adjustment or Titration, Methods of Terminating Treatment :

Patients receiving Gemcitabine should be monitored prior to each dose for platelet, leukocyte and granulocyte counts and, if necessary, the dose of Gemcitabine may be either reduced or withheld in the presence of haematological toxicity, according to the following scale:

Absolute granulocyte count (x10^9/L)		Platelet count (x10^9/L)	% of full dose
≥1000	And	≥100,000	100
500 to 1000	Or	50,000 to 99,999	75
<500	Or	<50,000	hold

Periodic physical examination and checks of renal and hepatic function should be made to detect non-haematologic toxicity. Dosage reduction with each cycle or within a cycle may be applied based on the amount of toxicity experienced by the patient. Doses should be withheld until toxicity has resolved in the opinion of the physician.

Gemcitabine 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 can be easily administered on an outpatient basis.

Elderly Patients : Gemcitabine has been well tolerated in patients over the age of 65. There is no evidence to suggest that dose adjustments, other than those recommended for all patients, are necessary in the elderly, although Gemcitabine clearance and half-life are affected by age.

Renal and Hepatic Impairment : Gemcitabine should be used with caution in patients with impaired renal function or hepatic insufficiency, as there is insufficient information from clinical studies to allow clear recommendation for this patient population. Mild to moderate renal insufficiency (GFR from 30 mL/min to 80 mL/m in) has no consistent, significant effect on Gemcitabine pharmacokinetics.

Children : Gemcitabine has been studied in limited Phase I and II trials in children in a variety of tumour types. These studies did not provide sufficient data to establish the efficacy and safety of Gemcitabine in children. Or, as directed by the registered physicians.

Reconstitution: Cytogem injection : For reconstitution 25 mL of 0.9% sodium chloride solution is added to the 1 gm vial.

Cytogem-200 injection : For reconstitution 5 ml of 0.9% sodium chloride solution is added to the vial.

Side Effects : Haematological Toxicity : Because Gemcitabine is a bone marrow suppressant, anaemia, leukopenia, and thrombocytopenia can occur as a result of administration of Gemcitabine. Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count. While two-thirds of patients experience some anaemia, only 7% have haemoglobin levels drop below 8 g/100 mL. While 19% of patients received transfusions, only 0.2% of patients discontinued because of anaemia. The white blood cell count is depressed in 61 % of patients, however only 9% of patients experience WBC's below 2000 cells/mm^3 and only 0.1% discontinued for leukopenia. Sixty-four percent of patients have reduced granulocyte counts and almost 25% drop below 1000 cells/mm^3. Platelet counts are reduced in 21% of patients but only 5% of patients experience counts below 50,000 cells/mm^3 and only 0.4% of patients were discontinued due to thrombocytopenia. Previous therapy with cytotoxic agents appears to increase the frequency and severity of the leukopenia, granulocytopenia, and thrombocytopenia. There is no evidence of cumulative haematological toxicity. Anaemia is manageable with the use of conventional transfusions. Dose reduction or omission may be necessary for severe leukopenia or thrombocytopenia. Rare cases of haemorrhage occurring simultaneously with thrombocytopenia have been reported, but were usually thought to be disease-related. Thrombocythemia is also commonly reported (7.5% of patients), but no patients were discontinued for this event. Febrile neutropenia is also commonly reported.

Hepatic Toxicity : Abnormalities of liver transaminase enzymes occur in about two-thirds of patients, but they are usually mild, non- progressive, and rarely necessitate stopping treatment. Less than 10% of patients experience elevations greater than 5 times normal and only 0.5% of patients were discontinued for abnormalities in liver function. One patient was discontinued for liver failure, but the assessment was complicated by a history of chronic alcoholism. Alanine transaminase (ALT) effects decline over time despite continued treatment. Elevations of alkaline phosphatase greater than 5 times normal occurred in 6.6% of patients but may have been due to bone disorders. Bilirubin values greater than 5 times normal were observed in 1.5% of patients, but ninety percent of patients had normal bilirubin levels.

Gastrointestinal : Nausea, and nausea accompanied by vomiting are each reported in about one-third of patients, respectively. This adverse event requires therapy in about 20% of patients, is rarely dose-limiting, and is easily manageable with standard antiemetics. Only 0.9% of patients report intractable vomiting and only 0.9% of patients discontinued due to nausea and vomiting. Diarrhoea and stomatitis are commonly reported. Diarrhoea (transient to tolerable) was reported by 7% of patients. Intolerable diarrhoea requiring therapy was reported in 0.5% of patients. No patients discontinued treatment because of diarrhoea.

Genito-Urinary Toxicity : Mild proteinuria and haematuria are reported in approximately half the patients, but are rarely clinically significant, and are not usually associated with any change in serum creatinine or blood urea nitrogen. However, a few cases (0.6% of patients) of renal failure of uncertain aetiology have been reported hence Gemcitabine should be used with caution in patients with impaired renal function. Rare cases (0.4%) of possible haemolytic uraemic syndrome have been reported. Cumulative renal toxicity has not been observed.

Pulmonary Toxicity : Dyspnoea occurring within hours following Gemcitabine injection is reported by approximately 10% of patients. This dyspnoea is usually mild and short-lived, rarely dose-limiting, and usually abates spontaneously without any specific therapy. The mechanism of this toxicity is unknown and the relationship to Gemcitabine is not clear. Only 0.6% of patients discontinued due to dyspnoea and only 0.1 % of these were believed to be medicine-related. Interstitial pneumonitis has been reported infrequently.

AllergicToxicity : A rash is seen in approximately 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Discontinuations for cutaneous toxicity were reported for only 0.3% of patients. Gemcitabine is well tolerated during the infusion with only a few cases of injection site reaction reported. Gemcitabine does not appear to be a vesicant. There have been no reports of injection site necrosis. Bronchospasm is usually mild and transient, but parenteral therapy may be required. Gemcitabine should not be administered to patients with a known hypersensitivity to the medicine.

Neurotoxicity : Mild to moderate somnolence occurs in approximately 10% of patients. Only 0.1 % of patients discontinued for somnolence. Asthenia is frequently reported with other flu symptoms but is also reported as an isolated symptom. Asthenia was cause for discontinuation by 1.4% of patients. Paresthesias are reported in 3.4% of patients, but only 0.2% report these as severe.

Oedema/Peripheral Oedema : Oedema/peripheral oedema is reported by approximately 30% of patients. Some cases of facial oedema have also been reported. Pulmonary oedema was reported infrequently (1%). Oedema/peripheral oedema is usually mild to moderate, rarely dose-limiting, is sometimes reported as painful and is usually reversible after stopping Gemcitabine treatment. The mechanism of this toxicity is unknown. However, it was not associated with any evidence of cardiac, renal or hepatic failure. Oedema resulted in the discontinuation of 0.7% of patients.

Alopecia : Overall, 86.7% of patients had no hair loss at all. Minimal to moderate hair loss was reported by 13% of patients. Only 0.5% of patients reported complete but reversible alopecia.

Contraindication : It is contraindicated in patients with known hypersensitivity to Gemcitabine or any other components of this product.

Use in pregnancy and lactation : Pregnancy Category D. Gemcitabine should be used during pregnancy. It is not known whether Gemcitabine is excreted in human breast milk.

Drug Interactions : No confirmed interactions have been reported with the use of Gemcitabine. No specific drug interaction studies have been conducted.

Precautions : Caution should be exercised when using Gemcitabine in patients with the risk of Schedule-dependent Toxicity, Myelosuppression, Pulmonary Toxicity and Respiratory Failure, Hemolytic Uremic Syndrome, Hepatic Toxicity, Embryofetal Toxicity, Radiation Therapy Toxicity and Impairment of Fertility.

Overdose : 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.

Storage : Store the vial in original carton at 20° - 25° C, away from light. Do not refrigerate as crystallisation may occur. Keep out of the reach of children.

Packing : Cytogem injection : Each box contains one vial of Gemcitabine Hydrochloride USP 1 gm lyophilized for injection.

Cytogem-200 injection : Each box contains one vial of Gemcitabine Hydrochloride USP 200 mg lyophilized powder for injection.

Cytogem

Gemcitabine Hydrochioride USP

DRUG INTERNATIONAL LTD.