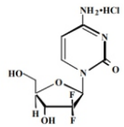
Job Size : 180 (L) X 222 (H)

Gemcitabine Injection 38 mg/ml concentrate for solution

GEMWEM® RTU
1000mg/200mg Injection

COMPOSITION
Each ml Contains:
Gemcitabine hydrochloride IP
equivalent to Gemcitabine…38 mg
Excipients….q.s.

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



The empirical formula for Gemcitabine HCl is $C_9H_{11}F_2N_3O_4$• HCl. It has a molecular weight of 299.66.

CLINICAL PHARMACOLOGY
Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary.
Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

MECHANISM OF ACTION
First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self 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.

PHARMACOKINETIC:

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

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m2. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

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

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

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

Age	Clearance Men (L/hr/m²)	Clearance Women (L/hr/m²)	Half-Life* Men (min)	Half-Life* Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

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

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

Drug Interactions
When Gemcitabine for Injection (1250 mg/m2 on Days 1 and 8) and cisplatin (75 mg/m2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m2 and on Day 8 was 107 L/hr/m2. The clearance of cisplatin in the same study was reported to be 3.94 mL /min/m2 with a corresponding half-life of 134 hours [see Drug Interactions (7)]. Analysis of data from metastatic breast cancer patients shows that, on average, Gemcitabine for Injection has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of Gemcitabine for Injection. Data from NSCLC patients demonstrate that Gemcitabine for Injection and carboplatin given in combination does not alter the pharmacokinetics of Gemcitabine for Injection or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

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

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

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

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

DOSAGE & ADMINISTRATION
Gemcitabine should only be prescribed by a physician qualified in the use of anti-cancer chemotherapy.

Ovarian Cancer
Recommended Dose and Schedule
The recommended dose of Gemcitabine Injection is 1000 mg/m2 as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after Gemcitabine Injection administration on Day 1 of each 21-day cycle.

Breast Cancer
Recommended Dose and Schedule
The recommended dose of Gemcitabine Injection is 1250 mg/m2 intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m2 on Day 1 as a 3 hour intravenous infusion before Gemcitabine Injection administration.

Non-Small Cell Lung Cancer
Recommended Dose and Schedule
Every 4-week schedule The recommended dose of Gemcitabine Injection is 1000 mg/m2 intravenously over 30 minutes on Days 1, 8, and 15 in combination with cisplatin therapy. Administer cisplatin intravenously at 100 mg/m2on Day 1 after the infusion of Gemcitabine Injection.

Pancreatic Cancer
Recommended Dose and Schedule
The recommended dosage of Gemcitabine Injection is 1000 mg/m2 intravenously over 30 minutes.
The recommended treatment schedule is as follows:
-Weeks 1 to 8: weekly dosing for the first 7 weeks followed by one week rest.
-After week 8: weekly dosing on Days 1, 8, and 15 of each 28-day cycle.

Combination use
The recommended dose for gemcitabine is 1,250 mg/m^2 body surface area given as a 30-minute intravenous infusion on Days 1 and 8 of the treatment cycle (21 days). Dosage reduction with each cycle or within a cycle may be applied based upon the grade of toxicity experienced by the patient.
Cisplatin has been used at doses between 75-100 mg/m^2 once every 3 weeks.

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

WARNINGS & PRECAUTIONS
Schedule-Dependent Toxicity: Increased toxicity with infusion time greater than 60 minutes or dosing more frequently than once weekly.
Myelosuppression: Monitor for myelosuppression prior to each cycle and reduce or withhold dose for severe myelosuppression.
Severe Cutaneous Adverse Reactions (SCARs): Permanently discontinue Gemcitabine for Injection if SCARs occur.
Pulmonary Toxicity and Respiratory Failure: Discontinue Gemcitabine Injection for unexplained dyspnea or other evidence of severe pulmonary toxicity.
Hemolytic Uremic Syndrome (HUS): Monitor renal function prior to initiation and during treatment. Discontinue Gemcitabine Injection for HUS or severe renal impairment.
Hepatic Toxicity: Monitor hepatic function prior to initiation and during treatment. Discontinue Gemcitabine Injection for severe hepatic toxicity.
Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential to use effective contraception.
Exacerbation of Radiation Therapy Toxicity: May cause severe and life-threatening toxicity when administered during or within 7 days of radiation therapy.
Capillary Leak Syndrome: Discontinue Gemcitabine Injection.
Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue Gemcitabine Injection.

DRUG INTERACTIONS
No specific interaction studies have been performed.
Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

ADVERSE EFFECTS
The most common adverse reactions for the single agent (≥20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

Use in Special Populations

Pregnancy[1]
Data on the use of gemcitabine in pregnant women are very limited. A case report described administration of gemcitabine for gallbladder cancer during pregnancy resulting in a healthy infant with no acute or late adverse effects during follow-up. Caution is advised. Pregnancy testing should be considered for females of reproductive potential prior to initiating therapy.

Lactation[2]
There are no data on the presence of gemcitabine in human milk or its effects on a breastfed infant. Caution is advised. Breastfeeding should be discontinued during treatment and for at least one week after the last dose.

Pediatric Use[3]
The safety and efficacy of gemcitabine in pediatric patients are not established.

- **Clinical Evidence:** A Phase II study in pediatric patients with relapsed acute lymphoblastic leukemia and acute myelogenous leukemia determined the maximum tolerated dose to be 10 mg/m^2/min over 360 minutes weekly for three weeks, followed by a one-week rest period. Toxicities included myelosuppression, febrile neutropenia, elevated transaminases, nausea, and rash/desquamation. No significant clinical activity was observed.

Renal and Hepatic Impairment[4]
Gemcitabine is primarily metabolized in the liver.

- **Renal Impairment:** Limited data suggest mild to moderate renal impairment does not significantly affect gemcitabine pharmacokinetics; caution is advised in severe renal impairment.
- **Hepatic Impairment:** Clearance may be reduced in patients with elevated bilirubin or transaminases, and hematologic toxicity may increase; caution and dose modification are advised in moderate to severe hepatic impairment.

Reference:

1. Diciolla A, Gianoni M, Fleury M, Szturz P, Demartines N, Peters S, Duran R, Desseauve D, Panchaud MA, Fasquelle F, Digklia A. Gallbladder cancer during pregnancy treated with surgery and adjuvant gemcitabine: A case report and review of the literature. Front Oncol. 2022;12:1006387. doi:10.3389/fonc.2022.1006387. PMID: 36353558.

2. Gemcitabine. Drugs and Lactation Database (LactMed). Bethesda (MD): National Library of Medicine (US); 2006–. PMID: 30000025.

3. Cole PD, Schwartz CL, Drachtman RA, de Alarcón PA, Chen L, Trippett TM. Phase II study of weekly gemcitabine and vinorelbine for children with recurrent or refractory Hodgkin's disease: a Children's Oncology Group report. J Clin Oncol. 2009;27(9):1456–1461. doi:10.1200/JCO.2008.20.3778. PMID: 19224841.

4. Venook AP, Egorin MJ, Rosner GL, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol. 2000;18(14):2780–2787. doi:10.1200/JCO.2000.18.14.2780. PMID: 10894879.

Storage : Store at temperature below 25^{0}C. Protected from moisture.
DO NOT REFRIGERATE.

Marketed by :
wembrace®
Wembrace Biopharma Pvt. Ltd.
B-6/5, First Floor, Okhla Industrial Area,
Phase 2, New Delhi 110020
Good To Talk
WEMBRACE CONSUMER CARE
EMAIL:-WECARE@WEMBRACE.IN
TOLL FREE CUSTOMER CARE :-18002029010
Mfd. by : Albino Lifesciences Pvt. Ltd.
(WHO-GMP Certified Company)
Village: Gaunspura, P.O.: Noorpur Bet,
Hamiran, Ludhiana-141008
Connect with us
® : Registered Trademark
30 EXCELLENT YEARS
ISO 9001