TAJ PHARMA

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Rx Gemcitabine for Injection USP 1000 mg

Gemcitabine for Injection USP 200 mg/ 1000 mg / 1400 mg
Gemcitabine™ 200/1000/1400

Rx only
COMPOSITION:

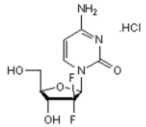
Gemcitabine™ 200	
Gemcitabine for injection USP 200 mg	
Each sterile Lyophilized vial contains	
Gemcitabine Hydrochloride USP	
Equivalent to Gemcitabine	200mg
Mannitol BP	200mg
Sodium Acetate BP	12.5mg
Excipients	q.s.

Gemcitabine™ 1000	
Gemcitabine for injection USP 1000 mg	
Each sterile Lyophilized vial contains	
Gemcitabine Hydrochloride USP	
Equivalent to Gemcitabine	1000mg
Mannitol BP	1000mg
Sodium Acetate BP	62.5mg
Excipients	q.s.

Gemcitabine™ 1400	
Gemcitabine for injection USP 1400 mg	
Each sterile Lyophilized vial contains	
Gemcitabine Hydrochloride USP	
Equivalent to Gemcitabine	1400mg
Mannitol BP	1400mg
Sodium Acetate BP	87.5mg
Excipients	q.s.

DESCRIPTION

Gemcitabine Hydrochloride is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCL is 2'-deoxy-',2'-diflurocytidine monohydrochloride (L-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. The clinical formula is supplied in a sterile form for intravenous use only. Vials of Gemcitabine contain either 200mg or 1 g or 1.4 g of gemcitabine HCL formulated with mannitol and sodium acetate as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

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. 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.

Pharmacokinetics

Gemcitabine position was studied in 5 patients who received a single 1000 mg/m^2/30 minutes infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine pharmacokinetics is linear and is described by a 2-compartment model. Population pharmacokinetics analyses of combined single and multiple dose studies showed that the volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations.

INDICATIONS AND USAGE

Non-small cell lung cancer: Gemcitabine is indicated in combination with cisplatin for the first-line treatment of patients with inoperable locally (stage IIIA or IIIB) or metastatic (stage IV) non-small cell lung cancer.
Pancreatic cancer: Celzor 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 is indicated for patients previously treated with 5-FU.

CONTRAINDICATION

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

DOSAGE AND ADMINISTRATION

Gemcitabine is for intravenous use only.

Adults
Single-agent use
Pancreatic cancer: Gemcitabine should be administered by intravenous infusion at dose of 1000mg/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 hematological toxicity experienced by the patient (see warnings). Patients receiving Gemcitabine 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 1.

Table 1 Dosage Reduction Guidelines

Absolute granulocyte count	Platelet count	% of full dose
(x 10^6 / L)	(x 10^6 / L)	
> 1,000 and	> 100,000	100
500-999 or	50,000-99,000	75
<500 or	<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 should be administered with caution in patients with evidence of significant renal or hepatic impairment.

Patients treated with Gemcitabine who complete on 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, respectively. And if non-hematologic toxicity has not been greater than WHO grade 1, and patients tolerate the subsequent course of Gemcitabine 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 100,000x 10^6/L, respectively, and that non-hematologic toxicity has not been greater than WHO grade 1.

Combination use

Non-small cell lung cancer:
Two schedules have been investigated and the optimum schedule has not been determined. With the 4-week schedule, Gemcitabine should be administered intravenously at 1000mg/m^2 over 30 minutes on days 1, 8, and 15 of each 28-day cycle. Cisplatin at a dose of 100mg/m^2 on day 1 after the infusion of Gemcitabine.

With the 3-week schedule, Gemcitabine should be administered intravenously at 1250mg/m^2 over 30 minutes on days 1 and 8 of each 21-day cycle. Cisplatin at a dose of 100mg/m^2 should be administered intravenously after the infusion of Gemcitabine on Day 1.

Dose Modification:
Dosage adjustments for hematologic toxicity may be required for Gemcitabine and for cisplatin. Gemcitabine dosage adjustment for hematological toxicity is based on the granulocyte and platelet counts taken on the day of therapy. Patients receiving Gemcitabine 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 1. For cisplatin dosage adjustment, see manufacturer's prescribing information. In general, for severe (grade 3 or 4) non-hematological toxicity, expect alopecia and nausea / vomiting, therapy with Gemcitabine plus cisplatin should be held or decreased 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 ¾ serum creatinine toxicity for Celzor plus cisplatin was 5% versus 2% for cisplatin alone).

OVERDOSAGE

There is no known antidote for overdose of Gemcitabine. Myelosuppression, paresthesia and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by I.V. 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.

Instructions for use/handling
The recommended diluents for reconstitution of Gemcitabine are 0.9% sodium chloride injection without preservatives. Due to solubility considerations, the maximum concentration for Gemcitabine upon reconstitution is 40mg/ml. Reconstitution at concentration greater than 40mg/ml may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5ml of 0.9% sodium chloride Injection to the 200mg vial or 25ml of 0.9% sodium chloride injection to the 1 g vial or 35ml of 0.9% sodium chloride injection to the 1.4g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38mg/ml which includes accounting for the displacement volume of the lyophilized powder (0.26ml for the 200mg vial or 1.3ml for the 1 g vial or 1.82ml for the 1.4g vial). The total volume upon reconstitution will be 5.26ml or 26.3ml or 36.82ml, respectively. Complete withdrawal of the vial contents will provide 200mg or 1g or 1.4g 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 Celzor is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% sodium chloride injection, the p^H 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 permits. If particulate matter or discoloration is found, do not administer.**

When prepared as directed, Gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25° c (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur.
The compatibility of Gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Caution should be exercised in handling and preparing Gemcitabine solutions. The use of gloves is recommended. If Gemcitabine 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 been observed in animal studies, two of three rabbits exhibited drug-related systematic toxicities (death, hypoactivity, nasal discharge, shallow breathing) due to dermal absorption.

WARNINGS

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

Bone marrow function:
Gemcitabine can suppress bone marrow function as manifested by leucopenia, thrombocytopenia, and anemia (see adverse reactions), and myelosupression is usually the dose limiting toxicity. Patients should be monitored for myelosupression during therapy and dosage adjusted.
Hemolytic-Uremic Syndrome (HUS) has been reported rarely with the use of Celzor.

Pregnancy:
Category D. Gemcitabine is fetotoxic causing fetal malformations. 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

General: A physician experienced in the use of cancer chemotherapeutic agents should monitor patients receiving therapy with Gemcitabine closely. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

Laboratory Tests: Patients receiving Gemcitabine 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 (see dosage and administration). 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 induced forward mutations in vitro in mouse. Studies have shown that Gemcitabine decreases fertility in male mice. In female was not affected but affected but maternal toxicities and fetotoxicity or embryo lethality were observed.

Nursing mothers: It is not known whether Gemcitabine or its metabolites are excreted in human milk. Because many 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 effected by age but there is no evidence, however, that unusual dose adjustment, (i.e., other than those already recommended in the dosage and administration section) are necessary in patient over 65.

Gender: Gemcitabine clearance is affected by gender however; there is no evidence that unusual dose adjustment is necessary in women.

Pediatric patients: Gemcitabine has not been studied in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Patients with renal or hepatic impairment; Gemcitabine should be used with caution in patients with preexisting renal impairment or hepatic insufficiency.

Drug Interactions: No confirmed interactions have been reported with the use of Gemcitabine.
Radiation Therapy: Safe and effective regimens for the administration of Gemcitabine with therapeutic doses of radiation have not yet been determined.

ADVERSE REACTIONS

Gemcitabine is used in a wide variety of malignancies, both as a single agent and in combination with other cytotoxic drugs.

Hematologic: Myelosuppression is the principal dose-limiting toxicity with Gemcitabine therapy. Dosage adjustments for hematologic toxicity are frequently needed. Anemia, leucopenia, or thrombocytopenia may occur.
Gastrointestinal: Nausea, vomiting, and diarrhea were commonly reported but were usually of mild to moderate severity.

Hepatic: Gemcitabine is associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there is no evidence of increasing hepatic toxicity with greater total cumulative dose.

Renal: Mild proteinuria and hematuria are commonly reported. Clinical findings consistent with the hemolytic uremic syndrome (HUS) may be reported.
The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolytic as indicated by elevation of billirubin 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.

Cardiovascular: Rarely cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension may be reported. Many of these patients may have a prior history of cardiovascular disease.

Others: Fever, rash, dyspnea, and oedema, flu-like symptoms, alopecia, and paresthesia may be reported.
There is an increased incidence of myelosuppression, anemia, nausea and vomiting when combination of Gemcitabine and cisplatin is used.

STORAGE: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not refrigerate after reconstitution.

HOW SUPPLIED

Gemcitabine™ 200
Gemcitabine for injection USP 200mg, as lyophilized powder in a single use vial, individually packaged in a carton.

Gemcitabine™ 1000
Gemcitabine for injection USP 1000mg, as lyophilized powder in a single use vial, individually packaged in a carton.

Gemcitabine™ 1400
Gemcitabine for injection USP 1400mg, as lyophilized powder in a single use vial, individual packaged in a carton.

SHELF LIFE
24 Months

Manufactured in India by:
TAJ PHARMACEUTICALS LTD.
Mumbai, India
at SURVEY NO.188/1 TO 189/1,190/1 TO 4,
ATHIYAWAD, DABHEL, DAMAN- 396210 (INDIA)

This leaflet was last revised in May 2019.

Rx Gemcitabine for Injection USP 1000 mg

TAJ PHARMA