Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

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Gemcitabine for Injection USP

Lyophilised

ATSURE® 200/1g/1.4g

L¦OvrÉÉU 200/1a¢ÉÉqÉ/1.4a¢ÉÉqÉ

ATSURE® 200
Each vial contains
Gemcitabine Hydrochloride USP
equivalent to Gemcitabine 200 mg

Reconstitute with 5ml of sodium chloride injection (0.9%W/V) and
shake gently to make a clear solution containing 38 mg/ml to 40 mg/ml of Gemcitabine.

Solution with precipitate to be discarded. Discard unused portion.

ATSURE® 1g
Each vial contains
Gemcitabine Hydrochloride USP
equivalent to Gemcitabine 1 g

Reconstitute with 25ml of sodium chloride injection (0.9%W/V) and
shake gently to make a clear solution containing 38 mg/ml to 40 mg/ml of Gemcitabine.

Solution with precipitate to be discarded. Discard unused portion.

ATSURE® 1.4g
Each vial contains
Gemcitabine Hydrochloride USP
equivalent to Gemcitabine 1.4 g

Reconstitute with 35ml of sodium chloride injection (0.9%W/V) and
shake gently to make a clear solution containing 38 mg/ml to 40 mg/ml of Gemcitabine.

Solution with precipitate to be discarded. Discard unused portion.

Do not inject without prior dilution. For Intravenous infusion only.

DESCRIPTION
Gemcitabine HCl is a nucleoside analogue that exhibits antitumor activity. 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 solvents.

CLINICAL PHARMACOLOGY
MECHANISM OF ACTION
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. 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 CEMT lymphoblastoid cells, Gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

PHARMACOKINETICS
Gemcitabine pharmacokinetics is linear and is described by a 2-compartment model. Gemcitabine half-life for short infusions ranged from 32 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of Gemcitabine for any given dose. The volume of distribution was increased with infusion length. Volume of distribution of Gemcitabine was 50 L/m^2 following infusions lasting <70 minutes, indicating that Gemcitabine, after short infusions is not extensively distributed into tissues. For long infusions, the volume of distribution dose to 370 L/m^2 reflecting slow equilibrium of Gemcitabine within the tissue compartment.
The effects of significant renal or hepatic insufficiency on the disposition of Gemcitabine have not been assessed.

The active metabolite, Gemcitabine triphosphate can be extracted from peripheral blood mononuclear cells. The half life of the terminal phase for Gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

INDICATIONS AND USAGE
1. 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.
2. Non-Small Cell Lung Cancer
   Gemcitabine is indicated in combination with cisplatin for the first-line treatment of patients with inoperable locally advanced (Stage III A or IIIB) or metastatic (Stage IV) non-small cell lung cancer.
3. Pancreatic Cancer
   Gemcitabine 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.
4. Bladder Cancer
   Gemcitabine alone or in combination is indicated for the treatment of patients with locally advanced or metastatic transitional call carcinoma (TCC) of the bladder.
5. 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.

DOSAGE AND ADMINISTRATION
Adults
Single-Agent Use
1. Pancreatic Cancer
   Gemcitabine should be administered by intravenous infusion at a dose of 100 mg/m^2 over 30 minutes once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding 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.

Combination Use:

2. 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 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. With the 3-week schedule, Gemcitabine 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 on Day 1.

3. Breast Cancer
   Gemcitabine 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 mglm^2 on Day 1 as a 3-hour. In general, for severe (Grade 3 or 4) non-hematological toxicity, except alopecia and nausea/vomiting, therapy with Gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician.

Dose Modification
Dosage adjustment in cases of Pancreatic cancer, Non small cell lung cancer and Breast cancer 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 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 Adjustment

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	Percentage of standard dose of Gemcitabine (%)
>1,000	and	>100,000	100
500 – 1,000	or	50,000 – 100,000	75
<500	or	<50,000	Hold

4. Ovarian Cancer:
   Gemcitabine should be administered intravenously at a dose of 1000 mg/m2 over 30 minutes on Days I and 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after Gemcitabine administration.

Dose Modifications
Gemcitabine 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 dosage should be modified according to guidelines in Table 2.

Table 2: Day 8 Dosage Reduction Guidelines for. Gemcitabine in Combination with carboplatin

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Absolute granulocyte count ($x 10^6$/L)		Platelet count ($x 10^6$/L)	Percentage of standard dose of Gemcitabine (%)
>1,500	and	>100,000	100
1,00 - < 1,500	or	75,000 – 100,000	50
<1,000	or	< 75,000	Hold

Gemcitabine may be administered on an outpatient basis.

INSTRUCTIONS FOR USE
The recommended diluent for reconstitution of Gemcitabine is 0.9% w/v Sodium Chloride Injection without preservatives. Reconstitute with Sodium chloride as given below and shake gently to make a clear solution containing 38mg/ml to 40mg/ml of Gemcitabine.

Gemcitabine	200mg	1gm	1.4gm
Sodium chloride	5ml	25ml	35ml

Solution with precipitate should be discarded. Discard unused portion.

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 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

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

SIDE EFFECTS
Hypoplasia of bone marrow (Myelosuppression) is the principal dose-limiting effect with Gemcitabine therapy. Anemia, leukopenia, thrombocytopenia and-other hematologic disorders have been reported in various studies. However, the overall hematologic toxicity of Gemcitabine must be considered modest, even with higher doses of their drug.

Mild blood loss and petechiae have occurred with Gemcitabine therapy.

In general, thrombocytopenia has been a mild effect of Gemcitabine therapy. The incidence of thrombocytopenia has been low (1.2% of patients or less), with mild, symptoms, which have not been clinically significant. Capillary leak syndrome, hypertension and edema have also been reported. Isolated cases of severe hypertension have been reported during Gemcitabine therapy. Paresthesias, somnolence have been reported with therapeutic use. Fever has been reported frequently with therapeutic use and generally not associated with clinical Infection. Nausea vomiting, diarrhoea, constipation and mucous membrane disorders have been reported following routine Gemcitabine therapy. Proteinuria and hematuria are frequently reported with Gemcitabine therapy. Nephrotoxicity and hemolytic uremic syndrome have been rarely reported. Transient elevations of serum transaminases have occurred frequently with patients, but patients remained asymptomatic. Mild dyspnea has been repored frequently following therapy. Several cases of pneumatics, pulmonary hemorrhage and fatal pulmonary toxicity manifesting as adult. respiratory distress syndrome (ARDS) as have also occurred. Alopecia and rashes seem to occur relatively frequently during Gemcitabine therapy. Case reports of pruritus, radiation recall dematitis, erythema, skin ulcerations, and pseudolymphoma have been noted with patients. Asthenia and bone pain has occurred with Gemcitabine therapy.

WARNINGS
Caution:
If the Infusion time is prolonged beyond 60 minutes and frequency is more than weekly then there is an increase in toxicity.

Gemcitabine suppresses bone marrow function. Manifestations of bone marrow suppression are leukopenia, thrombocytopenia and anemia. Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for Myelosuppression during therapy.

Gemcitabine is cautiously administered to pregnant women. There are no studies of Gemcitabine in pregnant women.

Gemcitabine use has been shown to cause pulmonary lung toxicity. The condition can be ameliorated using early supportive care measures.

Renal failure or Hemolytic uremic syndrome (HUS) have been reported with Gemcitabine use.

PRECAUTIONS
General:
A physician experienced in the use of cancer chemotherapeutic agents should do close monitoring of patients receiving therapy with Gemcitabine.

Laboratory Tests:
Complete blood count (CBC), including differential and platelet count should be monitored prior to each dose for patients receiving Gemcitabine Prior to Initiation of therapy and periodically thereafter the Laboratory evaluation of renal and hepatic function should be performed.
Carcinogenesis, Mutagenesis, Impairment of Fertility: To evaluate the carcinogenic potential of Gemcitabine, long-term animal studies have not been conducted

Pregnancy: Category D
Nursing Mothers:
The excretion kinetics of Gemcitabine or its metabolites inhuman milk is unknown. Because of the potential for serious adverse reactions from Gemcitabine in nursing infants, the mother should be,wamed 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:
Age affects the clearance of Gemcitabine. There is no evidence, that unusual dose adjustments are necessary in patients over 65. In the elderly, Grade 3 / 4 thrombocytopenia are more common.

Gemcitabine clearance is affected by gender. Older women were more likely not to proceed to a subsequent cycle and to experience grade 3/4 neutropenia and thrombocytopenia. In single agent studies of Gemcitabine adverse reaction rates were similar in men and 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:
Caution should be exercised for use of Gemcitabine in patients with preexisting renal impairment or hepatic insufficiency. Gemcitabine has not been studied in patients with significant renal or hepatic impairment.

DRUG INTERACTIONS
Drug Interactions: No specific drug interaction studies have been conducted. For information on the pharmacokinetics of Gemcitabine and cisplatin in combination.

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):
Analysis of the data 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):
Pre clinical and clinical studies have shown that Gemcitabine has radiosensitizing activity. Subsequent studies have been reported and suggest that Gemcitabine administered at lower doses with concurrent radiotherapy has predictable and less severe toxicity.

STORAGE
Store below 25°C. Do not freeze. Do not refrigerate after reconstitution.

PRESENTATION
ATSURE® (Gemcitabine for Injection USP) is available in a vial containing Gemcitabine Hydrochloride USP equivalent to Gemcitabine 200mg ,1g, 1.4g / vial.

For further details, please contact:
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Electronics City,
Bangalore - 560 100. India

To report adverse events and/or product complaints visit our website www.biocon.com or call toll free No: 1800 102 9465 or e mail us at drugsafety@Biocon.com

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