PACKAGE INSERT

GEMEBINE - 200 / GEMEBINE - 1000

(Gemcitabine Powder for Solution for Infusion 200 mg/vial and 1 g/vial)

Gemcitabine Hydrochloride

For Intravenous Use Only

DESCRIPTION

Gemcitabine Hydrochloride is a nucleoside analogue that exhibits antitumor activity. Gemcitabine Hydrochloride is 2´-deoxy-2´,2´- difluorocytidine monohydrochloride (β isomer).

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

The clinical formulation is supplied in a sterile form for intravenous use only.

Dosage form:

Lyophillized powder for solution for infusion, For IV use only

Composition:

- Gemcitabine Powder for Solution for Infusion 200mg/vial
  Each vial contains:
  Gemcitabine Hydrochloride equivalent to
  Gemcitabine 200 mg
- Gemcitabine Powder for Solution for Infusion 1g/vial
  Each vial contains:
  Gemcitabine Hydrochloride equivalent to
  Gemcitabine 1000 mg

Product Description

A white to off white lyophilized powder in a clear glass vial.

Product description after reconstitution:

When reconstituted it gives a clear solution practically free from foreign particles with pH in between 2.7 to 3.3.

PHARMACOLOGICAL CLASSIFICATION:

Anti metabolite anti neoplastic agent.

PHARMACOLOGICAL ACTIONS:

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 CEM T lymphoblastoid cells, Gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, Gemcitabine showed 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 was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to Gemcitabine 4 hours before cisplatin produced the greatest interaction.

INDICATIONS AND USAGE

Therapeutic Indications

Gemcitabine is indicated for treatment of locally advanced or metastatic non-small cell -lung 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. Gemcitabine is indicated for the treatment of patients suffering from bladder cancer, at the invasive stage. Gemcitabine in combination with paclitaxel, is indicated for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/ neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated. Gemcitabine in combination with carboplatin, is indicated for the treatment of patients with recurrent epithelial ovarian carcinoma, who have relapse > 6 months, following platinum- base therapy.

CONTRAINDICATION

Gemcitabine is contraindicated in those patients with a known hypersensitivity to the drug. Concomitant administration of gemcitabine and radiotherapy, due to the risk of radiosensitization and of onset of severe pulmonary and oesophageal fibrosis. Cisplatin /Gemcitabine in patient with severe renal failure.

WARNINGS

Warnings

When used consecutively, the possibility of serious radiosensitization calls for an interval of at least 4-weeks between gemcitabine chemotherapy and radiotherapy. This interval can be shorter if required by the patient condition. Increased toxicity has been reported when infusion time is prolonged and recommended interval between doses is reduced.

Like other cytotoxic, gemcitabine can induce bone-marrow suppression, resulting in anaemia, leukopenia and thrombocytopenia. This thrombocytopenia is often severe and platelet transfusions can sometimes be necessary. However, the myelosuppression is of short duration and does not usually require dosage reduction, and rarely requires the discontinuation of treatment. Hypersensitivity: anaphylactic reaction has been rarely reported.

Precautions

Patients receiving gemcitabine must be closely monitored. A medical laboratory must check their biological parameters. Treatment may be required if the drug produces any toxic effects. In patients with impaired bone-marrow function, the treatment should be started with caution. As with other cytotoxic treatments, the risk of cumulative bone-marrow aplasia must be considered when gemcitabine treatment is given together with other chemotherapy.

Patients receiving gemcitabine must undergo haematological tests including blood cells and platelet count before each administration. It may be necessary to suspend or alter the treatment if bone-marrow toxicity induced by the drug is detected. Peripheral blood levels may continue to deteriorate after treatment has been stopped. Gemcitabine must be used with caution in patients with liver failure as no studies have been done in patients with hepatic impairment. Administration of Gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

Renal failure with creatinine clearance between 30 ml/min and 80 ml/min has no significant effect on the pharmacokinetics of gemcitamine. The use of gemcitabine should be avoided in pregnant or nursing women.

DRUG INTERACTIONS

When Gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of Gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours. Analysis of data from metastatic breast cancer patients shows that, on average, Gemcitabine 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. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

PREGNANCY:

Category D.

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.

ADVERSE REACTIONS

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

Single-Agent Use: Myelosuppression is the principal dose-limiting toxicity with Gemcitabine therapy. Dosage adjustments for hematologic toxicity are frequently needed.

All WHO-graded laboratory events are, regardless of causality. Non-laboratory adverse events discussed below were those reported, regardless of causality, for at least 10% of all patients, except the categories of Extravasation, Allergic, and Cardiovascular and certain specific events under the Renal, Pulmonary, and Infection categories.

Hematologic — Gemcitabine can induce bone-marrow suppression, resulting in anemia, leukocytopenia and thrombocytopenia. The bone-marrow suppression is usually mild and mostly affects the granulocyte count. Thrombocytosis is another commonly reported effect. Febrile neutropenia is also commonly reported.

Gastrointestinal — Nausea and vomiting were commonly reported but were usually of mild to moderate severity. Diarrhea and stomatitis.

Hepatic — Gemcitabine was associated with transient elevations of one or both serum transaminases , 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 (see Hepatic under Post-marketing experience).

Renal — Mild proteinuria and hematuria were commonly reported, but are rarely clinically significant. These conditions are usually not combined with changes in serum creatinine or uremia. However, some cases of renal failure on uncertain etiology have been reported. No cumulative renal toxicity has been observed. Gemcitabine therapy should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required (see Renal under Post-marketing experience).

Fever — Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — A rash can occur and can be associated with itching. The rash is usually mild, and does not necessitate dosage reduction and responds to local therapy. Desquamation, vesiculation and ulceration have occasionally been reported.

Pulmonary. 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.

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Edema — Edema, peripheral edema and generalized edema were reported.
Flu-like Symptoms — A Flu-like syndrome, which is rarely severe, can occur. It is generally of brief duration and rarely requires a dosage reduction. 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.
Infection — Infections were reported. Sepsis was rarely reported.
Alopecia — Hair loss, usually minimal.
Extravasation — Injection-site related events were reported. There were no reports of injection site necrosis. Gemcitabine is not a vesicant.
Allergic — Bronchospasm has sometimes been reported. Anaphylactoid reaction has been reported rarely. Gemcitabine should not be administered to patients with a known hypersensitivity to this drug.
Cardiovascular — Cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension have been reported. Many of these patients had a prior history of cardiovascular disease (see Cardiovascular under Post-marketing experience).

OVERDOSAGE

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/m² 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.

DOSAGE AND ADMINISTRATION

Gemcitabine is for intravenous use only.

Adults

Non small- cell lung cancer

Single agent use:

The recommended dose is 1000 mg/m², given by intravenous infusion.

The administration must be repeated once weekly for three weeks, followed by a one-week rest period. This four-week cycle is then repeated. A dose reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

Combination use:

Gemcitabine in combination with cisplatin can be administered using two dosage regimens one regimen use a three-week schedule, the other uses a four-week schedule.

The three-week schedule is usual regimen; this three-week cycle uses gemcitabine 1250mg/m² given by 30 minutes intravenous infusion on days 1 and 8, followed by one-week rest period. This three-week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

The four-week cycle uses gemcitabine 1000mg/m² given by 30 minutes intravenous infusion on days 1, 8 and 15, followed by one-week rest period. This four-week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

Pancreatic adenocarcinoma

The recommended dose is 1000 mg/m² given by 30 minutes intravenous infusion. This should be repeated once weekly for 7 weeks, followed by a week rest. Subsequent cycles should consist of injections once weekly for 3 consecutive weeks out of every 4 weeks. A dosage reduction or delay before each administration of the chemotherapy may be applied, based upon the amount of toxicity experienced by the patient.

Bladder cancer, at the invasive stage

The recommended dose of gemcitabine in combination with cisplatin, is 1000 mg/m²,given by 30 minutes intravenous infusion on days 1, 8 and 15, followed by one-week rest period for a 28 day cycle. Cisplatin is given at a recommended dose of 70 mg/m² on day 2. This four- week cycle is then repeated. A dosage reduction or delay before each administration of the chemotherapy 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/m².

Breast cancer

Paclitaxel (175 mg/m²) administered on Day 1 over approximately 3 hours as an intravenous infusion, followed by gemcitabine (1250 mg/m²) 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.

Ovarian cancer

Gemcitabine in combination with carboplatin is recommended using gemcitabine 1000 mg/m² 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 to attain a 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.

For all indications

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 hematologic toxicity, according to the following scale:

Absolute granulocyte count ($x10^6$/l)		Platelet count ($x10^6$/l)	% of total dose
>1,000	and	>100,000	100
500-1000	or	50,000-100,000	75
<500	or	<50,000	0

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

Elderly patients

Gemcitabine has been well tolerated by patients over 65 years of age. The pharmacokinetic data suggest that the metabolism of the drug is not affected by age.

Patients with hepatic or renal impairment

Gemcitabine should be used with caution in patents with hepatic insufficiency or with impaired renal function as there Is insufficient information from clinical studies to allow clear dose recommendation for this patient population. Mild to moderate renal insufficiency (GFR from 30mL/min to 80mL/min) 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 tumor types. These studies did not provide sufficient data to establish the efficacy and safety of Gemcitabine in children.

Method of Administration

Intravenous route.

Gemcitabine is well tolerated during infusion and is usually easy to administer. Reactions at the site of injection are rare: no case of cutaneous necrosis has been reported. If extravasation, the administration must be stopped immediately.

Handling

It is compulsory that injectable solutions of cytotoxic agents be prepared by specialized, trained staff with knowledge of the drugs used, under conditions which ensure protection of the environment, and particularly of the drug handling staff. Preparation requires a room reserved for this purpose. Smoking, eating and drinking are prohibited in this room. The handling staff must have a set of appropriate equipment for handling particular long-sleeved coats, protective masks, caps, protective goggles, sterile disposable gloves, worktop protection sheets and waste collection containers and bags. Excreta and vomitus must be handled with care. Pregnant women must be warned and avoid handling cytotoxic agents. All broken containers must be treated with the same precautions and regarded as contaminated waste. Contaminated waste is to be disposed of by incineration in rigid containers labeled for this purpose.

Instructions for Use/Handling:

The recommended diluent for reconstitution of Gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Although no incompatibility has been demonstrated, it is none-the-less recommended that mixing gemcitabine solutions with those of other drugs should be avoided. Due to solubility considerations, the maximum concentration for Gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.To reconstitute, add at least 5 ml of 0.9% Sodium Chloride Injection to the 200 mg vial and at least 25 ml of 0.9% Sodium Chloride Injection to the 1000 mg vial. Shake to dissolve. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection.Parenteral drugs should be inspected visually for particulate matter and discoloration, prior to administration.As other cystostatics, Gemcitabine hydrochloride must be handled with care. Unused products must be destroyed according to hospital procedures of cytotoxic waste deal.

PRESENTATION:

Vials:

Gemcitabine Powder for Solution for Infusion 200mg/vial-200 mg white, lyophilized powder in a 10-mL size (sterile single use vial) USP Type I clear tubular glass vial with 20 mm grey bromobutyl lyophilized rubber stopper and 20 mm aluminium flip off lavender seal

Gemcitabine Powder for Solution for Infusion 1g/vial-1 g white, lyophilized powder in a 50-mL size (sterile single use vial) USP Type I clear tubular glass vial with 20 mm grey bromobutyl lyophilized rubber stopper and 20 mm aluminium flip off lavender seal

STORAGE:

Store below 30°C. Do not refrigerate. Discard any unused portion.

When prepared as directed, Gemcitabine solutions are stable for 24 hours at below 30°C. Discard unused portion. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur.

Unopened vials of Gemcitabine are stable until the expiration date indicated on the package when stored at below 30°C.

Manufactured by :

INTAS

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