Religem™

RELIC
Biotechnology Pvt. Ltd.
An ISO 9001:2008 Certified Company

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℞ For the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

GEMCITABINE FOR INJECTION USP

Religem™

200mg / 1g /1.4g
Lyophilized for Injection

For IV Use

Composition :
Religem - 200mg / 1g / 1.4g
Each Single dose Lyophilized vial contains :

Gemcitabine Hydrochloride USP	
Equivalent to Gemcitabine	200 mg / 1g / 1.4g
Mannitol IP	200 mg / 1g / 1.4g

Description :
Religem (gemcitabine HCl) is a novel nucleoside analogue that exhibits antitumor activity. Chemically gemcitabine HCl is 2' deoxy-2', 2' – difluorocytidine monohydrochloride (Beta-isomer) Empirical formula for Gemcitabine HCl is $C_9H_{11}F_2N_3O_4$. HCl. Molecular weight: 299.66

CLINICAL PHARMACOLOGY :
Mechanism of Action: Gemcitabine is a nucleoside analog that exhibits antitumor activity. It exhibits cell specificity, primarily killing cells undergoing DNA synthesis in the S-phase. It also blocks the progression of cells through the G1/S-phase boundary. The cytotoxic activity is attributed to its active metabolites, diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleotides. First Gemcitabine diphosphate inhibits ribonucleotide reductase, which catalyses the reactions that generate the deoxynucleoside triphosphate for DNA synthesis. Inhibition of this enzyme causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands causing inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair growing DNA strands (masked chain termination).

PHARMACOKINETICS :
Absorption/Distribution : Patients receiving gemcitabine 1000mg/m^2 once weekly generally demonstrate C_{max} values of 10-40 mg/L and achieve steady state after 15-30 mins, during 30min infusion protocol. Plasma protein binding of gemcitabine is negligible. A volume of distribution of 50 L/m^2 indicated that it is not extensively distributed into tissues following short infusions (< 70 mins). For long infusions, the volume of distribution is 370 L/m^2 reflecting slow equilibrium with the tissue compartment.

Metabolism/Excretion :
It is metabolised intracellularly to the active diphosphate and triphosphate nucleotides. Clearance & elimination half-life is affected by gender & age, but this does not require dosing adjustments. Half-life ranges from 32-94 mins for short infusions & 245-638 mins. for long infusions. The terminal phase half-life for the triphosphate metabolite from mononuclear cells ranges from 1.7-19.4 hrs. A small amount (<10%) of gemcitabine is excreted unchanged in urine.

INDICATIONS :

- NSCLC: First-line therapy for locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) NSCLC.
- Pancreatic Cancer: Treatment for locally advanced (nonresectable Stage II or III) or metastatic (Stage IV) adenocarcinoma of the pancreas indicated for patients who have been previously treated with 5-FU.
- Carcinoma of bladder: Treatment of metastatic bladder (urothelial) cancer.
- Breast Cancer: Indicated alone or in combination with other chemotherapeutic agents in the management of patients with advanced or metastatic breast cancer.
- Ovarian and epithelial Cancer: Indicated, alone or in combination with other chemotherapeutic agents in the management of patients with advanced or relapsed epithelial ovarian cancer.

CONTRAINDICATIONS :

Religem is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS :

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

Hematology : Religem can suppress bone marrow function. Patients should be monitored for myelosuppression during therapy.

Pulmonary : Pulmonary toxicity has been reported with the use of Gemcitabine.

Renal: Hemolytic Uremic Syndrome (HUS) &/or renal failure have been reported following 1 or more doses of Gemcitabine .

Hepatic : Serious hepatotoxicity including liver failure & death has been reported very rarely in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs.

PREGNANCY: Pregnancy Category D Gemcitabine can cause foetal harm when administered to a pregnant woman.

PRECAUTIONS :

Monitoring: Monitor patients prior to each dose with a complete CBC including differential and platelet count.

Hepatic and renal: Perform laboratory evaluations of renal & hepatic function prior to initiation of therapy & periodically thereafter.

ADVERSE EFFECTS :

Neutropenia was observed as the dose limiting factor of Gemcitabine. Common adverse effects in clinical trials included nausea & vomiting (69%) fever (41%) odema or fluid retention (up to 34%) rash (30%) & flu-like symptoms (19%). Only about 10% of all subjects participating in gemcitabine clinical trials discontinued therapy due to side effects. Hair loss was reported in 15% of subjects. This side effect was reversible & none of the subjects experienced complete hair loss from their treatment.

DRUG INTERACTIONS :

No Specific drug interaction study of Gemcitabine has been conducted.

OVERDOSAGE :

Myelosuppression, paresthesias & 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 mins every 2 weeks to several patients in Phase 1 study. There is no known antidote for overdosage of gemcitabine. In the event of suspected overdose, the patient should be monitored with appropriate blood counts & should receive supportive therapy, as necessary.

DOSAGE AND ADMINISTRATION :

Religem is recommended for IV use only. Religem may be administered in an outpatient basis.

Pancreatic cancer :

Single - agent use for adults: Administer IV at a dose of 1000 mg/m^2 over 30 mins once weekly for up to 7 weeks (or until toxicity necessitates reducing or holding a dose), followed by 1 week of rest from treatment. Infuse subsequent cycles once weekly for 3 consecutive weeks out of every 4 weeks.

Dosage Modification : Dosage adjustment is based upon the degree of hematologic toxicity

experienced by the patient. Monitor patient prior to each dose with CBC. If marrow supression is detected therapy should be modified/suspended according to the guidelines in Table 1:

Table 1: Gemcitabine Dosage Reduction Guidelines

Absolute granulocyte count ($x 10^6$/L)		Platelet count ($x 10^6$/L)	% of full dose
≥ 1000	and	≥ 100,000	100
500-999	or	50,000-99,000	75
<500	or	<50,000	Hold

Patients treated with Religem who complete an entire cycle of therapy may have the dose for subsequent cycles increased by 25%, provided that the AGC & platelet nadirs exceed $1500x10^6$/L & $100,000x10^6$/L respectively & if non-hematologic toxicity has not been greater than WHO Grade 1.

NSCLC : Combination use with Cisplatin-Two schedules have been investigated & the optimum schedule has not been determined:

· **4 - week schedule** :Religem should be administered IV at 1000 mg/m^2 over 30 mins. on Days 1,8 & 15 of each 28 day cycle. Administer Cisplatin IV at 100 mg/m^2 on day 1 after the infusion of Religem.

· **3 - week schedule** : Administer IV Lifogem at a dose of 1250 mg/m^2 over 30 mins. on days 1 & 8 of each 21 day cycle Administer Cisplatin IV at a dose of 100 mg/ m^2 after the infusion of Lifogem on Day 1.

Dose Modifications : Dosage adjustment to based on the degree of hematologic toxicity experienced by the patient. Monitor patient prior to each dose with CBC (see Table 1). For severe (Grade 3 or 4) non-hematologic toxicity, except alopecia, & nausea-vomiting, therapy with Lifogem plus cisplatin should be held or decreased by 50% depending on the judgement of the treating physician.

Bladder Carcinoma : IV infusion of Religem (over 30 min) at a dose of 1000-1200 mg/m^2 once week for 3 weeks, followed by a 1 week rest.

Breast carcinoma : Religem should be administered intravenously at a dose of 1250 mg/m^2 over 30 mins. on Days 1 & 8 of each 21-day cycle. Paclitaxel should be administered at 175 mg/m^2 on Day 1 as a 3-hr IV infusion before Religem administration. Patients should be monitored prior to each dose with a CBC, including differential counts. Patients should have an AGC of $1500x10^6$/L & a platelet count of 100,000 x 10^6/L prior to each cycle. Doses of 600 (with cisplatin) or 800-1250 mg/m^2 by IV infusion once a week for 2/3 weeks followed by a 1 week rest.

Dose Modifications :Religem dosage adjustments for hematological toxicity is based on the granulocyte & platelet counts taken on Day 8 of therapy. If marrow suppression is detected, Religem dosage should be modified according to the guidelines in Table 2.

Table 2: Day 8 Dosage Reduction Guidelines for Religem in Combination with Paclitaxel

Absolute granulocyte count ($x 10^6$/L)		Platelet count ($x 10^6$/L)	% of full dose
≥ 1200	and	≥ 75,000	100
1000-1199	or	50,000-75,000	75
700-999	and	≥ 50,000	50
<700	or	<50,000	Hold

Ovarian Cancer :Religem should be administered intravenously at a dose of 1000 mg/m^2 over 30 mins on Days 1 & 8 of each 21-day cycle. Carboplatin AUC 4 should be administered intravenously on Day 1 after Religem administration. Patients should be monitored prior to each dose with a CBC, including differential counts. Patients should have AGC 1500 x 10^6/L & a platelet count 100,000 x 10^6/L prior to each cycle.

Dose Modifications :Religem 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,Religem dosage should be modified according to guidelines in Table 3.

Table 3: Day 8 Dosage Reduction Guidelines for Religem in Combination with Carboplatin

Absolute granulocyte count (x 10^6/L)		Platelet count (x 10^6/L)	% of full dose
≥ 1500	and	≥ 100,000	100
1000-1499	and/or	75,000-99,999	50
<1000	and/or	<75,000	Hold

In general, for severe (Grade 3 or 4) non-hematological toxicity, except nausea/vomiting, therapy with Religem should be held or decreased by 50% depending on the judgment of the treating physician. For carboplatin dosage adjustment, see manufacturer's prescribing information.

Dilution : Diluent for reconstitution of Religem is 0.9% sodium chloride injection without preservatives. Because of solubility consideration, the maximum concentration for Religem upon reconstitution is 40 mg/ml. Avoid reconstitutions at concentrations >40mg/ml. This may lead to incomplete reconstitution.

Reconstitution : To reconstitute add 5ml of 0.9% Sodium Chloride injection to the 200 mg vial or 25 ml of 0.9% Sodium chloride injection to the 1 g vial. Shake to dissolve. These dilutions each yield a Gemcitabine concentration of 40mg/mL. The appropriate amount of drug may be administered as prepared by further diluting with 0.9% sodium chloride injection to concentration as low as 0.1mg/ml. Do not refrigerate solutions of reconstituted Religem,as crystallization may occur.

When prepared as directed, Religem solutions are stable for 24 hours at controlled room temperature 20°C to 25°C. Discard unused portion. Solutions of reconstituted Religem should not be refrigerated, as crystallization may occur.

Handling : Caution should be exercised in handling and preparing Religem solutions. The use of gloves is recommended. If Religem solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water.

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

STORAGE :

Store at controlled room temperature of 20^{0}C to 25 ^{0}C.

PRESENTATION :

Religem lyophilized injection is available in a strength of 200mg & 1g & 1.4g as a single vial in a box.