Relitaxel™

30 mg / 100 mg / 260 mg /300 mg

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

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

For the use only of Registered Medical Practitioner or a Cancer Hospital or a Laboratory

℞

PACLITAXEL INJECTION I.P.

Relitaxel™

30 mg / 100 mg / 260 mg /300 mg **For IV Use**

COMPOSITION

Each ml contains :

Paclitaxel I.P.	6 mg
Polyoxyl 35 Castor Oil USNF	527 mg
Dehydrated Alcohol I.P.	49.7% v/v

DESCRIPTION **Relitaxel** (Paclitaxel) Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous Infusion. **Relitaxel** is available in 30 mg (5 mL), 100 mg (16.7 mL), and 260 mg (43.4 mL) multidose vials.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

PHARMACOKINETICS

Following intravenous administration of **Relitaxel**, paclitaxel plasma concentrations declines in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 mcg/mL, indicate that between 89-98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15-275 mg/m^2 doses of **Relitaxel** as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance.

Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6-hydroxypaclitaxel, accounted for the balance. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6, 3'-p-dihydroxypaclitaxel, by CYP3A4.

INDICATIONS

Relitaxel is indicated, after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

Relitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Relitaxel is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

DOSAGE AND ADMINISTRATION

All patients should be premedicated prior to **Relitaxel** administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before **Relitaxel** , diphenhydramine (or its equivalent) 50 mg I.V 30 to 60

minutes prior to **Relitaxel**, and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes before In patients previously treated with chemotherapy for ovarian cancer, the recommended regimen is **Relitaxel** 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with carcinoma of the breast, **Relitaxel** at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective after failure of chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

For patients with AIDS-related Kaposi's sarcoma, **Relitaxel** administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended.

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

Reduce the dose of dexamethasone as one of the three premedication drugs to 10 mg PO (instead of 20 mgPO);

Initiate or repeat treatment with **Relitaxel** only if the neutrophil count is at least 1000 cells/ mm^3.

Preparation for Intravenous Administration : Relitaxel must be diluted prior to infusion. **Relitaxel** should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle.

Stability : Unopened vials of **Relitaxel** Injection are stable until the date indicated on the package when stored between 20°- 25° C (68°-77 F), in the original package. Upon refrigeration components in the **Relitaxel** vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

SIDE EFFECTS

Toxicity was more pronounced in the study utilizing **Relitaxel** at a dose of 135 mg/m^2 every 3 weeks than in the study utilizing **Relitaxel** at a dose of 100 mg/m every 2 weeks. Notably, severe neutropenia, febrile neutropenia, and opportunistic infections were more common with the former dose and schedule.

Patients with AIDS-related Kaposi's sarcoma have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care.

Hematologic : Bone marrow suppression was the major dose-limiting toxicity of **Relitaxel**. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible.

Fever was frequent. Infectious episodes occurred and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Hypersensitivity Reactions : All patients received premedication prior to **Relitaxel**

The frequency and severity of HSRs were not affected by the dose or schedule of **Relitaxel** (paclitaxel) Injection administration.

The minor hypersensitivity reactions consisted mostly of flushing, rash , hypotension, dyspnea, tachycardia and hypertension . The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as proof of the continuing surveillance of **Relitaxel** safety.

Cardiovascular : Hypotension, Bradycardia during the first 3 hours of infusion, occurred.

Significant cardiovascular events included syncope, rhythm abnormalities, hypertension and venous thrombosis. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECGs at baseline, prior therapy with

anthracyclines did not influence the frequency of ECG abnormalities. **Relitaxel**.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported es. Rare reports of atrial fibrillation and supraventricular tachycardia have been received as proof of the continuing surveillance of **Relitaxel** safety.

Respiratory : Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as proof of the continuing surveillance of **Relitaxel** safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Neurologic: Peripheral neuropathy was observed without preexisting neuropathy.

The frequency of peripheral neuropathy increased with cumulative dose.

Arthralgia/ Myalgia : The symptoms were usually transient, occurred two or three days after **Relitaxel** administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic : Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as proof of the continuing surveillance of **Relitaxel** safety.

Renal : Among the patients treated for Kaposi's sarcoma with **Relitaxel**, five patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other four patients had renal insufficiency with reversible elevations of serum creatinine.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site.

DRUG INTERACTIONS

Doses of **Relitaxel** and Cisplatin given as sequential infusions, myelosuppression was more profound when **Relitaxel** was given after Cisplatin than with the alternate sequence (i.e.**Relitaxel** before Cisplatin).

The metabolism of **Relitaxel** is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

In the absence of formal clinical drug interaction studies, caution should be exercised when administered **Relitaxel** concomitantly with known substrates and inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema and generalized urticaria have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine and H_2antagonists. Patients who experience severe hypersensitivity reactions to **Relitaxel** should not be rechallenged with the drug.

Relitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells / mm^3. Frequent monitoring of blood counts should be instituted during **Relitaxel** treatment.

If patients develop significant conduction abnormalities during **Relitaxel** infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with **Relitaxel**.

PRECAUTIONS

Note : Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. Diluted **Relitaxel** solution should be stored in bottles (glass, polypropylene) or plastic bags and administered through polyethylene lined administration sets.

Preparation and Administration Precautions : Relitaxel is a cytotoxic anticancer drug, caution should be exercised in handling **Relitaxel**. The use of gloves is recommended. If **Relitaxel** solutions contacts the skin, wash the skin immediately and thoroughly with soap and water. If **Relitaxel** contacts mucous membranes, the membrane should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea has been reported.

Relitaxel contains dehydrated alcohol USP, consideration should be given to possible CNS and other effects of alcohol.

Hematology : Relitaxel therapy should not be administered to patients with baseline neutrophil counts of

less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving **Relitaxel** . Patients should not be re-treated with subsequent cycles of **Relitaxel** until neutrophils recover to a level > 100,000 cells/mm^3. In the case of severe neutropenia (< 500 cells/mm^3 for severe days or more during a course of **Relitaxel** therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor risk AIDS related Kaposi's sarcoma. **Relitaxel**, at recommended dose for this disease, can be initiated and repeated if the neutrophil count is atleast 1000 cells/mm^3.

Nervous system : Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of **Relitaxel**.

Relitaxel contains dehydrated alcohol USP, 396 mg/ml; consideration should be given to possible CNS and other effects of alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of **Relitaxel** has not been studied.

Paclitaxel has been shown to be clastogenic in vitro. Paclitaxel was not mutagenic in the Ames test.

Usage in Pregnancy

Relitaxel can cause foetal harm when administered to a pregnant women.

There are no adequate and well-controlled studies in pregnant women. If **Relitaxel** is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Usage in Nursing Mothers

It is not known whether the drug is excreted in human milk.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving **Relitaxel** therapy.

Pediatric use

The safety and effectiveness of **Relitaxel** in pediatric patients have not been established.

OVERDOSAGE

There is no known antidote for **Relitaxel** overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

CONTRAINDICATIONS

Relitaxel is contraindicated in patients who have history of hypersensitivity reactions to **Relitaxel** or other drugs formulated in polyoxyethylated castor oil.

STORAGE

Store below 25°C. Protect from light. DO NOT FREEZE.

PRESENTATION

Each box containing single multidose vial of 30 mg/5 ml.

Each box containing single multidose vial of 100 mg/16.7 ml.

Each box containing single multidose vial of 260 mg/43.4 ml.

Each box containing single multidose vial of 300 mg/50 ml.