PRODUCT PRESCRIBING INFORMATION

NAME OF THE DRUG

PACLIAVENIR SOLUTION FOR INJECTION

(Paclitaxel)
6mg/mL

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

PACLIAVENIR SOLUTION FOR INJECTION (PACLITAXEL) SHOULD BE ADMINISTERED UNDER THE SUPERVISION OF A PHYSICIAN EXPERIENCED IN THE USE OF CANCER CHEMOTHERAPY AGENTS.

PATIENTS RECEIVING PACLIAVENIR SOLUTION FOR INJECTION MUST BE PRE-TREATED WITH CORTICOSTEROIDS, ANTIHISTAMINES, AND H_2 ANTAGONISTS (SUCH AS DEXAMETHASONE, DIPHENHYDRAMINE AND CIMETIDINE OR RANITIDINE) TO MINIMIZE HYPERSENSITIVITY REACTIONS (SEE DOSAGE AND ADMINISTRATION). SEVERE HYPERSENSITIVITY REACTIONS CHARACTERIZED BY DYSPNEA AND HYPOTENSION REQUIRING TREATMENT, ANGIOEDEMA, AND GENERALIZED URTICARIA HAVE OCCURRED IN PATIENTS RECEIVING PACLITAXEL. THESE REACTIONS ARE PROBABLY HISTAMINE MEDIATED. RARE FATAL REACTIONS HAVE OCCURRED IN PATIENTS DESPITE PRE-TREATMENT. PATIENTS WHO EXPERIENCE SEVERE HYPERSENSITIVITY REACTIONS TO PACLITAXEL SHOULD NOT BE RECHALLENGED WITH THE DRUG.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

ACTION AND CLINICAL PHARMACOLOGY

PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganization of the microtubules 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.

In vitro, paclitaxel exhibits cytotoxic activity against a wide variety of both human and rodent tumour cell lines.

Pharmacokinetics

The pharmacokinetics of Paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m^2, and infusion schedules ranging from 3 to 24 hours. Following intravenous administration of paclitaxel the drug exhibited a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The latter phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3.0 to 52.7 hours, and total body clearance has ranged from 11.6 to 24.0 L/h/m^2. Mean steady state volume of distribution has ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

Following 3 hour infusion of 175 mg/m^2, mean terminal half-life was estimated to be 9.9 hours; mean total body clearance was

12.4 L/h/m^2.

Variability in systemic paclitaxel exposure, as measured by AUC ($_{0-4}$) for successive treatment courses was minimal; there was no evidence of accumulation of paclitaxel with multiple treatment courses.

The pharmacokinetics of paclitaxel have been shown to be non-linear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose-related decrease in total body clearance. These findings are most readily observed in patients in whom high plasma concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings.

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

The distribution and metabolism of paclitaxel *in vivo* has not been fully elucidated. High concentrations of paclitaxel and its metabolites have been reported in the bile of patients treated with the drug. Mean (standard deviation) values for urinary recovery of unchanged drug following 6-,11-, and 24-hour infusions at doses of 15 to 275 mg per square meter of body surface ranged from 1.3% (±0.5%) to 12.6% (±16.2%) of the dose, indicating extensive nonrenal clearance. The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been fully elucidated.

Clinical Studies

Breast carcinoma
The safety and efficacy of PACLIAVENIR SOLUTION FOR INJECTION in patients with advanced breast cancer unresponsive to usual treatments were evaluated in a Phase II, multi-center, non-randomized open-label trial. PACLIAVENIR SOLUTION FOR INJECTION was infused continuously for a minimum of 3 hours every three weeks at a dose of 175 mg/m^2. Doses were reduced from 175 mg/m^2 to 135 mg/m^2 and 100 mg/m^2 in the event of toxicity. Dose escalation to 200 mg/m^2 was used in the absence of toxicity. A total of 36 patients were evaluated for safety and 27 for efficacy. The overall response rate was 27%, with a complete response reported at 4%, partial response at 19%, stable disease was seen in 51%, and disease progression was reported in 26%. Time-to-progression was assessed in 22 patients, with a median progression free survival of 83 days. The median survival for all registered and assessable patients was 102 days and 231 days, respectively.

Lung carcinoma

The safety and efficacy of PACLIAVENIR SOLUTION FOR INJECTION in patients with metastatic or locally advanced non-small-cell lung cancer not subject to curative treatment were evaluated in a Phase II, multi-center, non-randomized, open-label-trial. PACLIAVENIR SOLUTION FOR INJECTION was infused continuously for a minimum of 3 hours every three weeks at a dose of 175 mg/m^2 to 200 mg/m^2. Dose escalation to 200 mg/m^2 and 225 mg/m^2 was used in the absence of toxicities. A total of 60 patients with advanced or metastatic non-small cell lung cancer were enrolled in this study. The overall response rate for registered patients was 25%. Time-to-progression was assessed in 52 patients at 125 days. Median survival was reported for all registered and assessable patients at 204 and 237 days, respectively.

INDICATIONS AND CLINICAL USE

Paclitaxel is indicated alone or in combination, for the treatment of advanced carcinoma of the ovary.
For the treatment of metastatic breast cancer after failure of combination chemotherapy.
Prior therapy should have included an anthracycline unless clinically contraindicated.
Advanced non-small cell lung cancer:
Paclitaxel, associated with cisplatinum is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.
Keposi's sarcoma:
Paclitaxel is indicated in the second-line treatment of AID'S related Kaposi's sarcoma.
Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.
For the treatment of advanced gastric carcinoma.

CONTRAINDICATIONS

PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or other drugs formulated in Polyoxyl 35 castor oil.

PACLIAVENIR SOLUTION FOR INJECTION should not be used in patients with severe baseline neutropenia (<1 500 cells/mm^3)

PACLIAVENIR SOLUTION FOR INJECTION is contraindicated in patients with severe hepatic impairment.

PACLIAVENIR SOLUTION FOR INJECTION is also contraindicated in patients with concurrent, serious, uncontrolled infections.

WARNINGS

PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapy agents.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration

PACLIAVENIR SOLUTION FOR INJECTION should be administered as a diluted infusion. Patients receiving PACLIAVENIR SOLUTION FOR INJECTION should be pretreated with corticosteroids, antihistamines, and H_2 antagonists (such as dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions (see DOSAGE AND ADMINISTRATION). Anaphylaxis, and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in patients receiving paclitaxel. These reactions are probably histamine-mediated. Literature reports indicate that rare fatal reactions have occurred in patients despite pre-treatment. In case of a severe hypersensitivity reaction, PACLIAVENIR SOLUTION FOR INJECTION infusion should be discontinued immediately and the patient should not be rechallenged with the drug (see ADVERSE REACTIONS).
Patients should be observed closely during the initial cycles of treatment. Appropriate supportive therapies should be readily available in case of a severe hypersensitivity reaction.
PACLIAVENIR SOLUTION FOR INJECTION should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. Bone marrow suppression (primarily neutropenia) is dose and schedule dependent and is the dose-limiting toxicity within a regimen. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted during PACLIAVENIR SOLUTION FOR INJECTION treatment. Patients should not be retreated with subsequent cycles of PACLIAVENIR SOLUTION FOR INJECTION until neutrophils recover to a level >1,500 cells/mm^3, and platelets recover to a level >100,000 cells/mm^3 (see DOSAGE AND ADMINISTRATION).

Paclitaxel should be given before a platinum compound when it is .given in combination with a platinum compound.

Severe cardiac conduction abnormalities have rarely been reported during paclitaxel therapy. If patients develop significant conduction abnormalities during administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with PACLIAVENIR SOLUTION FOR INJECTION (see ADVERSE REACTIONS).

Moderate to severe mucositis is uncommon with the recommended dose and schedule of paclitaxel. However, if treatment is to be continued in the event of moderate or severe reactions, the dose of paclitaxel should be reduced for subsequent courses of paclitaxel therapy. In KS patients, severe mucositis is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

<u>Use in Pregnancy</u>

PACLIAVENIR SOLUTION FOR INJECTION may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryototic and fetotoxic in rabbits and to decrease fertility in rats. There are no studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with PACLIAVENIR SOLUTION FOR INJECTION.

<u>Nursing Mothers</u>

It is not known whether PACLIAVENIR SOLUTION FOR INJECTION is excreted in human milk. Breast feeding should be

discontinued for the duration of PACLIAVENIR SOLUTION FOR INJECTION therapy.

Fertility

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Use in Children

The safety and effectiveness of PACLIAVENIR SOLUTION FOR INJECTION in pediatric patients have not been established.

PRECAUTIONS

Undiluted concentrate should not come in contact with plasticized polyvinyl chloride (PVC) equipment. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate)], which may leach from PVC infusion bags or sets, diluted PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) solutions should preferably be stored in glass bottles and administered through polyethylene-lined administration sets.

Cardiovascular

Hypotension, hypertension and bradycardia have been observed during PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) administration; patients are usually asymptomatic and generally do not require treatment. In severe cases paclitaxel infusions may need to be interrupted or discontinued at the discretion of the treating physician. Frequent monitoring of vital signs, particularly during the first hour of PACLIAVENIR SOLUTION FOR INJECTION infusion is recommended. Continuous cardiac monitoring is not required except for patients who develop serious conduction abnormalities (see WARNINGS, ADVERSE REACTIONS).

Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual. A dose reduction of 20% is recommended for all subsequent courses of PACLIAVENIR SOLUTION FOR INJECTION for moderate to severe neuropathy (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

Hepatic

There is evidence that the toxicity of PACLIAVENIR SOLUTION FOR INJECTION is enhanced in patients with increased liver enzymes. Caution should be exercised when administering PACLIAVENIR SOLUTION FOR INJECTION to patients with moderate to severe hepatic impairment and dose adjustments should be considered (see ADVERSE REACTIONS).

Other

A combination of pulmonary radiotherapy and paclitaxel treatment (irrespective of the order of the treatments) may promote the development of interstitial pneumonitis.

Gastrointestinal
Pseudomembranous colitis has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.

Drug Interactions

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP 3A4 and CYP 2C8. Caution should be exercised when administering paclitaxel concomitantly with known substrates, inducers or inhibitors of these isoenzymes.

Doxorubicin: Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered BEFORE doxorubicin and using longer than recommended infusion times (Paclitaxel administered over 24 hours; doxorubicin administered over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Cisplatin: myelosuppression was more profound and paclitaxel clearance was reduced by approximately 33% when

paclitaxel was given AFTER cisplatin than with the alternate sequence (i.e. paclitaxel BEFORE cisplatin).

Epirubicin: Reports in the literature suggest that plasma levels of epirubicinol, a metabolite of epirubicin, may be increased when paclitaxel and epirubicin are used in combination. The clinical significance of the increased epirubicinol plasma levels is unknown.

Montelukast should not be taken with Paclitaxel since it is known to be a potent in vitro inhibitor of the P450 2C8 enzyme, as well it may decrease the metabolic clearance of drugs that are primarily metabolized by the 2C8 pathway.

Driving/Operating Machinery

Since PACLIAVENIR SOLUTION FOR INJECTION contains ethanol, consideration should be given to the possibility of CNS and other effects.

ADVERSE REACTIONS

The incidence of adverse reactions in the table that follows are derived from ten clinical trials in carcinoma of the ovary and of the breast involving 812 patients treated with paclitaxel at doses ranging from 135-300 mg/m^2/day and schedules of three or twenty-four hours. Data from a subset of 181 patients treated with 175 mg/m^2 and a three-hour infusion schedule are also included in the table.

SUMMARY OF ADVERSE REACTIONS			
		135 to 300 mg/m^2 % of Patients (N=812)	175 mg/m^2 % of Patients (N=181)
Bone Marrow			
Neutropenia	< 2 000/mm^3	90	87
	< 500/mm^3	52	27
Leukopenia	< 4 000/mm^3	90	86
	< 1 000/mm^3	17	4
Thrombocytopenia	< 100 000 mm^3	20	6
	< 50 000 mm^3	7	1
Anemia	< 11 g/dL	78	62
	< 8 g/dL	16	6
Infections		30	18
Bleeding		14	9
Red Cell Transfusions		25	13
Red Cell Transfusions (normal baseline)		12	6
Platelet Transfusions		2	0
Hypersensitivity Reactions			
All		41	40
Severe		2	1
Cardiovascular			
Bradycardia during first 3 hours of infusion		3	3
Hypotension during first 3 hours of infusion		12	11
Severe cardiovascular events		1	2

Abnormal ECG All patients Patients with normal baseline	 23 14	 13 8
Peripheral Neuropathy Any symptoms Severe symptoms	 60 3	 64 4
Myalgia/Arthralgia Any symptoms Severe symptoms	 60 8	 54 12
Gastrointestinal Nausea and vomiting Diarhhea Mucositis	 52 38 31	 44 25 20
Alopecia	87	93
Hepatic (patients with normal baseline) Bilirubin elevations Alkaline phosphatase elevations AST elevations	 7 22 19	 4 18 18
Injection site reactions	13	4

The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting (286 patients treated in paclitaxel clinical studies and 812 patients treated in other clinical studies) .

The frequency of undesirable effects listed below is defined using the following convention: very common (≥1/10); common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

Infections and infestations:	*Very common*: infection (mainly urinary tract and upper respiratory tract infections including herpes simplex, oral candidiasis, pharyngitis, rhinitis), with reported cases of fatal outcome *Common:* flu syndrome *Uncommon*: severe infection, septic shock *Rare**: Sepsis pneumonia, peritonitis
Blood and the lymphatic system disorders:	*Very common*: myelosuppression, severe neutropenia, anaemia, thrombocytopenia, severe leucopenia, bleeding *Common:* neutropenic fever *Uncommon:* severe anaemia *Rare*: febrile neutropenia* *Very rare**: acute myeloid leukaemia, myelodysplastic syndrome

Immune system disorders:	*Very common*: minor hypersensitivity reactions (mainly flushing and rash) *Uncommon*: (delayed) hypersensitivity, significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension) *Rare**: anaphylactic reactions *Very rare**: anaphylactic shock (including fatal hypersensitivity)
Metabolism and nutrition disorders:	*Very common*: anorexia *Uncommon:* weight gain, weight loss *Not known*:* tumor lysis syndrome
Psychiatric disorders:	*Very rare**: confusional state
Nervous system disorders:	*Very common*: neurotoxicity (mainly: peripheral neuropathy), paraesthesia, somnolence *Common*: depression, severe neuropathy (mainly peripheral), nervousness, insomnia, abnormal thinking, hypokinesia, abnormal gait, hypoaesthesia, taste perversion *Rare**: motor neuropathy (with resultant minor distal weakness) *Very rare**: autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, acute encephalopathy, dizziness, ataxia, headache.
Eye disorders	*Uncommon:* dry eyes, amblyopia, visual field defect *Very rare**: optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended. Not known*: macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	*Very rare**: ototoxicity**,** sensorineuronal hearing loss, tinnitus, vertigo

Cardiac disorders:	*Common*: bradycardia, tachycardia, palpitation, syncope *Uncommon*: congestive heart failure, myocardial infarction**,** AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, *Rare:* cardiac failure *Vary rare**: atrial fibrillation supraventicular tachycardia.
Vascular disorders:	*Very common*: hypotension *Common:* vasodilatation (flushing) *Uncommon*: hypertension, thrombosis, thrombophlebitis *Very rare**: shock *Not known*: phlebitis
Respiratory, thoracic and mediastinal disorders:	*Common:* epistaxis *Rare**: respiratory failure. pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea pleural effusion, *Very rare**: cough, pulmonary hypertension
Gastrointestinal disorders:	*Very common*: diarrhoea, vomiting, nausea, mucosal inflammation, stomatitis, abdominal pain *Common:* dry mouth, mouth ulceration, melaena, dyspepsia *Rare**: bowel obstruction, bowel perforation, ischemic colitis, acute pancreatitis *Very rare**: mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, necrotising enterocolitis, ascites,oesophagitis, constipation.
Hepato-biliary disorders:	*Very rare**: hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	*Very common*: alopecia *Common*: transient and mild nail and skin change, dry skin, acne *Uncommon:* changes in nail pigmentation or discoloration of nail bed *Rare**: pruritus, rash**,** erythema *Very rare**: Stevens-Johnson syndrome, exfoliative dermatitis,- epidermal necrolysis, erythema multiforme, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet), folliculitis *Not known*: scleroderma

Musculoskeletal, connective tissue and bone disorders:	*Very common*: Arthralgia, myalgia *Common:* bone pain, leg cramps, myasthenia, back pain *Not known:* systemic lupus erythematosis
Renal and urinary disorders	*Common*: dysuria
General disorders and administration site conditions:	*Very common:* asthenia, pain, oedema including peripheral and face *Common*: mild injection site reaction (including localised oedema, pain, erythema, induration, tenderness, skin discoloration or swelling, on occasion extravasation, can result in cellulitis and skin fibrosis and skin necrosis), chest pain, chills *Rare*:* pyrexia, dehydration, asthenia, oedema, malaise.
Investigations:	*Common*: severe elevation in transaminases, AST (SGOT), severe elevation in alkaline phosphatase *Uncommon*: severe elevation in bilirubin *Rare**: increase in blood creatinine

The safety profile has been evaluated from a large randomized trial (paclitaxel 135 mg/m^2 over 24 hours with cisplatin 75 mg/m^2 versus cyclophosphamide/cisplatin) which included 410 patients, 196 of whom received paclitaxel. Use of paclitaxel with platinum agents has not resulted in any clinically significant changes to the safety profile of the product when used at the recommended dosage.

Summary of Three Hour Infusion Data at a Dose of 175 mg/m^2

Unless otherwise stated, the following safety data relate to sixty-two patients with ovarian cancer and 119 patients with breast cancer treated at a dose of 175 mg/m^2 and a three hour infusion schedule, in phase III clinical trials. All patients were premedicated to minimize hypersensitivity reactions. Bone marrow suppression and peripheral neuropathy were the principal dose-related adverse reactions. Further, as compared to a 24 hour infusion schedule, the incidence of neutropenia was less common when paclitaxel was administered as a three-hour infusion. Neutropenia was generally rapidly reversible and did not become worse with cumulative exposure. Repeated exposure increases the frequency of neurologic symptoms. None of the observed toxicities were influenced by age.

Hematologic

The most frequent notable undesirable effect of paclitaxel was bone marrow suppression. Severe neutropenia (< 500 cells/mm^3) occurred in 27% of patients, but was not associated with febrile episodes. Only one percent of patients experienced severe neutropenia for seven days or more. Neutropenia was not more frequent or severe in patients who received prior radiation therapy, nor did it appear to be affected by treatment duration or cumulative exposure. Eighteen percent of patients had an infectious episode, all non-fatal. Although severe septic episodes associated with severe neutropenia attributable to paclitaxel were reported in early clinical trials, no severe infections or septic episodes were seen at the recommended dose and infusion schedule. There were five fatal septic episodes associated with severe neutropenia attributable to paclitaxel in the overall 812 patient database.

Thrombocytopenia with platelet counts <100,000 cells/mm^3 was reported in six percent of patients. Thrombocytopenia with platelet counts <50,000 cells/mm^3 was reported in one percent of patients. Severe thrombocytopenia (<50,000 cells/mm^3) was observed during the first two courses only. Bleeding episodes occurred in nine percent of patients; no patient needed

platelet transfusion.

Anemia was seen in 62% of patients, but was severe (Hb<8 g/dL) in only 6% of patients. Incidence and severity of anemia are associated with baseline hemoglobin status. Red cell transfusions were required in 13% of patients (6% of those with normal baseline hemoglobin levels).

Hypersensitivity Reactions

Severe hypersensitivity reactions occurred in 1% of patients even with premedication. These reactions occurred generally in early treatment courses and within the first hour of infusion. Dyspnea, flushing, chest pain and tachycardia were the most frequent signs and symptoms.

The dosage and schedule had no effect on the frequency of hypersensitivity reactions which occurred in 21% of courses where patients were given the recommended dose at the recommended schedule. The majority of reactions were minor. The most frequent were flushing (28%), rash (14%), and hypotension (3%).

Cardiovascular

During infusion of paclitaxel, hypotension and bradycardia were experienced by 24% and 4% of patients, respectively, and did not usually occur during the same course; the majority of episodes were asymptomatic and did not require treatment.

One patient experienced transient hypertension during the second paclitaxel cycle. In addition, two patients experienced severe cardiovascular events (tachycardia and thrombophlebitis), possibly related to paclitaxel. None of these patients required discontinuation of treatment. In the same studies at a lower dose or longer infusion, three severe cardiovascular events (atrioventricular (AV) block, syncope and hypotension associated with coronary stenosis resulting in death) possibly related to paclitaxel administration were reported. Ten severe cardiovascular events occurred which included cardiac rhythm disturbance and syncope among the 812 patients (see WARNINGS).

An abnormal ECG occurred in 13% of patients during the clinical trials at a dosage of 175 mg/m^2 and a three-hour infusion schedule. Some patients (8%) with a normal ECG prior to study entry developed an abnormal tracing during the study. Of the 812 patients, the most frequently reported ECG changes were non-specific repolarization abnormalities, sinus tachycardia and premature beats. In most cases, there was no clear relationship between the administration of paclitaxel and ECG changes; these changes were of no, or minimal, clinical relevance.

Since the above summary, cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other prior chemotherapy especially anthracyclines.

Neurologic

Peripheral neuropathy, mainly manifested by paresthesia, affected 64% of patients, but was severe in only 4% of patients. Neurologic symptoms can occur following the first course and can worsen with increased exposure to paclitaxel. Peripheral neuropathy was the cause of drug discontinuation in three cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. Rare neurologic events include grand mal seizures and encephalopathy. Reports of motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension have also been observed. Optic nerve and/or visual disturbances (scintillation scotomata) have also been reported, especially in patients who have received higher doses than recommended. These effects have generally been reversible.

Arthralgia/Myalgia

Arthralgia or myalgia affected 54% of patients and was severe in 12% of patients. The symptoms usually were pain in the large joints of the arms and legs and were transient occurring two to three days after administration and resolving within a few days.

Alopecia

Alopecia was observed in nearly all patients.

Gastrointestinal

Gastrointestinal side effects were usually mild to moderate: nausea/vomiting (44%), diarrhea (25%) and mucositis (20%) were reported. Other gastrointestinal events included anorexia (25%), constipation (18%) and intestinal obstruction (4%). Neutropenic enterocolitis, bowel obstruction/perforation and ischemic colitis and pancreatitis have occurred.

Hepatic

In patients with normal baseline liver function, four percent had elevated bilirubin, 18% had elevated alkaline phosphatase, and 18% had elevated AST (SGOT). Severe elevations (>5x normal values) of bilirubin, alkaline phosphatase or AST were seen in 1%, 5%, and 5% of patients, respectively. There have been rare reports of hepatic necrosis and hepatic encephalopathy leading to death.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Dose adjustment is recommended. Patients should be monitored closely for the development of profound myelosuppression.

Injection Site Reactions

Phlebitis can occur following the intravenous administration of paclitaxel. Extravasation during intravenous infusion can lead to edema, pain, erythema and induration. Occasionally extravasation can result in cellulitis.
Skin discoloration can also occur. Recurrence of skin reactions at a site of previous extravasation following administration at a different site, so called "recall", has been reported rarely. A specific treatment of extravasation reactions is unknown, however treatment with a subcutaneous injection of hyaluronidase diluted in saline has been shown to be effective in a mouse skin model.

Other

Mild and transient nail and skin changes have been observed. Radiation pneumonitis has been reported in patients who have received concurrent radiotherapy.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash, pruritus, Stevens-Johnson syndrome and toxic epidermal necrolysis have been received as part of the continuing surveillance of paclitaxel safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety. In the phase 3 trial of paclitaxel 135 mg/m2 over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/cisplatin.

Accidental Exposure:
Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
The carcinogenic potential of paclitaxel has not been studied. Paclitaxel has been shown to be clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.
Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no known antidote for PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

DOSAGE AND ADMINISTRATION

Note: Undiluted concentrate should not come in contact with plasticized PVC equipment. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl) phthalate], which may be leached from PVC infusion bags or sets, diluted PACLIAVENIR SOLUTION FOR INJECTION (paclitaxel) solutions should preferably be stored in bottles (glass) and administered through polyethylene-lined administration sets.

PACLIAVENIR SOLUTION FOR INJECTION should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

All patients should be premedicated prior to PACLIAVENIR SOLUTION FOR INJECTION administration in order to prevent hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 to 6 hours before PACLIAVENIR SOLUTION FOR INJECTION, diphenhydramine 50 mg I.V. (or its equivalent), 30 to 60 minutes prior to PACLIAVENIR SOLUTION FOR INJECTION, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before PACLIAVENIR SOLUTION FOR INJECTION.

Preparation and Administration

Note: See WARNINGS, PRECAUTIONS and PHARMACEUTICAL INFORMATION for detailed instructions on the administration of PACLIAVENIR SOLUTION FOR INJECTION.

PACLIAVENIR SOLUTION FOR INJECTION must be diluted prior to infusion.

PACLIAVENIR SOLUTION FOR INJECTION is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling PACLIAVENIR SOLUTION FOR INJECTION. The use of gloves is recommended. Following topical exposure, tingling, burning, redness have been observed. If PACLIAVENIR SOLUTION FOR INJECTION solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If PACLIAVENIR SOLUTION FOR INJECTION solution contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been 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. It is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Advanced Carcinoma of the Ovary
For previously untreated patients with carcinoma of the ovary, PACLIAVENIR SOLUTION FOR INJECTION is administered intravenously at 21 day intervals by a continuous infusion over 24 hours at a dose of 135 mg/m2 followed by a dose of cisplatin at a dose of 75 mg/m2. In patients previously treated using chemotherapy for carcinoma of the ovary, PACLIAVENIR SOLUTION FOR INJECTION is administered at 21 day intervals over 3 hours at a dose of 135 mg/m2 or 175 mg/m2.

Breast carcinoma

Adjuvant Treatment of Node-Positive Breast Cancer
PACLIAVENIR SOLUTION FOR INJECTION is administered intravenously at 21 day intervals, by continuous infusion over 3 hours at a dose of 175 mg/m2, for four courses administered sequentially to doxorubicin-containing combination therapy.

For patients with advanced metastatic breast cancer, PACLIAVENIR SOLUTION FOR INJECTION is administered intravenously by continuous infusion over 3 hours at a dose of 175 mg/m^2 at 21 day intervals. Single courses of PACLIAVENIR SOLUTION FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000

cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3) or severe peripheral neuropathy during PACLIAVENIR SOLUTION FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLIAVENIR SOLUTION FOR INJECTION.

Non-Small Cell Lung Carcinoma

For patients with non-small cell lung carcinoma, PACLIAVENIR SOLUTION FOR INJECTION is administered intravenously by continuous infusion over 24 hours at a dose of 135 mg/m2 followed by cisplatin, 75mg/m² at 21 day intervals.

Single courses of PACLIAVENIR SOLUTION FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3) or severe peripheral neuropathy during PACLIAVENIR SOLUTION FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLIAVENIR SOLUTION FOR INJECTION.

AIDS Related Kaposi's Sarcoma

Paclitaxel is administered intravenously at either 21 day intervals over 3 hours at a dose of 135 mg/m^2, or at 14 day intervals over 3 hours at a dose of 100 mg/m^2 (dose intensity 45-50 mg/m^2/week). As with any patient showing signs of immunosuppression, the following modifications are recommended: Reduce dexamethasone premedication from 20 mg PO to 10 mg PO, initiate or repeat treatment with Paclitaxel only if the neutrophil count is at least 1000 cells/mm^3, reduce the dose of subsequent courses of Paclitaxel by 20% for patients who experience neutrophil counts of <500 cells/mm^3 for a week or longer, and initiate concomitant hematopoietic growth factor as clinically indicated.

For patients with Gastric Carcinoma,

Paclitaxel 210 mg/m^2 administered intravenously over 3 hours every 3 weeks. The dosage should be decreased according to patient's age and performance status. Single courses of PACLIAVENIR SOLUTION FOR INJECTION should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3) or severe peripheral neuropathy during PACLIAVENIR SOLUTION FOR INJECTION therapy should have the dosage reduced by 20% for subsequent courses of PACLIAVENIR SOLUTION FOR INJECTION.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name

Paclitaxel (USAN)

Chemical Name

Benezenepropanoic_acid,β-(benzoylamino)-α-hydroxy-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-*b*]oxet-9-yl ester, [2a*R*-[2aα,4β,4aβ,6β,9α(αR*,βS*),11α,12α,12aα,12bα]]-.

Physical Properties

Description: White to off white crystalline powder

Solubility: Paclitaxel is highly lipophilic and insoluble in water. It is slightly soluble in hexane and propylene glycol, sparingly soluble in t-butanol, and soluble in such solvents as Polyoxyl 35 castor oil , polyethylene glycols 300 and 400, ethanol, chloroform, toluene, acetone, methylene chloride and methanol.

Melting point: 216 – 217^{0}C

Empirical Formula

$C_{47}H_{51}NO_{14}$

Molecular Weight
853.9

Composition

Each mL of sterile nonpyrogenic solution contains 6 mg of paclitaxel, 527 mg of polyoxyl 35 castor oil and 49.7% (v/v) dehydrated alcohol.

Stability and Storage Recommendations

Unopened vials of PACLIAVENIR SOLUTION FOR INJECTION concentrate are stable until the date indicated on the package when stored under refrigeration, 2^0-25^0C in the original package. Do not freeze. The infusion must be initiated within 24 hours of reconstitution. The 50 mL bulk vial should be used within 8 hours after initial entry. The pH of PACLIAVENIR SOLUTION FOR INJECTION diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final concentration of 0.3 to 1.2 mg/mL remained within the range of 4.5 to 5.0 within a 24 hour period.

Reconstitution and Preparation of Dosage Form

NOTE: Due to the extracting effect of Polyoxyl 35 castor oil on plastics, polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion are not recommended. Contact of PACLIAVENIR SOLUTION FOR INJECTION with PVC causes leaching of DEHP [di-(2-ethylhexyl) phthalate]. Paclitaxel solutions should be stored in glass bottles and administered through polyethylene lined administration sets. It is recommended to filter the solution using in-line filters of 0.22 microns.

Preparation for i.v.

Administration: PACLIAVENIR SOLUTION FOR INJECTION must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection or in 5% Dextrose Injection to a final concentration of 0.3 to 1.2 mg/ml. It is recommended to filter the solution using in-line filters of 0.22 microns. The solutions are physically and chemically stable for up to 24 hours at below 25^0 C.
. The intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Special Instructions

Paclitaxel is a cytotoxic anticancer drug and is toxic in both concentrated and diluted form and must be handled and administered with care. Should accidental skin contact occur the affected part should be washed immediately with soap and water. If paclitaxel accidentally contacts eyes or mucous membranes, flush thoroughly with water.

Directions for Dispensing from Pharmacy Bulk Vial of 50 mL

The use of the Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture programme. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. Dispensing from the bulk vial should be completed within 8 hours at 25^0 C after initial entry.

AVAILABILITY OF DOSAGE FORMS

PACLIAVENIR SOLUTION FOR INJECTION is available in single dose vials of 5 mL and 16.7 mL, and pharmacy bulk vials of 50 mL containing respectively 30 mg, 100 mg and 300 mg paclitaxel at a concentration of 6mg/mL. Non-medicinal ingredients: dehydrated alcohol 49.7% v/v and Polyoxyl 35 castor oil.

Complete product monograph is available upon request.

REGISTRATION NUMBER: 130 89 30941 00

MANUFACTURER:
Biolyse Pharma
St Catharines Ontario, Canada L2S 3Y2

LICENSE HOLDER AND IMPORTER:
BioAvenir Ltd.
Kibutz Glil Yam 46905

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