Paclitaxel contains dehydrated alcohol IP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol.

Hepatic: There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times ULN**.**

Injection site reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

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.

Pediatric use: The safety and effectiveness of paclitaxel in pediatric patients have not been established.

OVERDOSAGES

There is no known antidote for paclitaxel overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neuropathy, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity.

STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77°F). Protect from light.
If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

PRESENTATION

PACLIWEL® is available as 30 mg / 5 ml, 100 mg / 16.7 ml, 260 mg / 43.4 ml and 300 mg / 50 ml single dose vials individually packed in carton.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of cytotoxic medicinal products should be followed.

Preparation and Administration Precautions: PACLIWEL® is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel 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.

Preparation for Intravenous Administration: PACLIWEL® must be diluted prior to infusion. PACLIWEL® should be diluted in 0.9 % sodium chloride injection: 5 % dextrose injection; 5 % dextrose and 0.9 % sodium chloride injection, or 5 % dextrose in Ringer's injection to a final concentration of 0.3 **-** 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability: Unopened vials of PACLIWEL® are stable until the date indicated on the package when stored between 20 **-** 25 °C, in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. 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.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V**,** Gurgaon - 122016, Haryana**,** India

Manufactured by:
Getwell Pharmaceuticals
474**,** Udyog Vihar, Phase-V**,** Gurgaon - 122016, Haryana**,** India

0700PWDM0613-00

GETWELL

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

Paclitaxel Injection IP

PACLIWEL®

Rx only

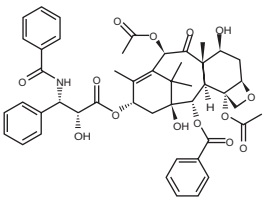
WARNING

PACLIWEL® (Paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in few patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. 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.

DESCRIPTION

PACLIWEL® (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. Paclitaxel is a natural product with antitumor. activity. Paclitaxel is obtained from Taxus species. Paclitaxel is available as 30 mg (5 ml), 100 mg (16.7 ml), 260 mg (43.4 ml) and 300 mg (50 ml) single dose vials.

CHEMICAL STRUCTURE



Molecular Weight - 853.93
Molecular Formulae - $C_{47}H_{51}NO_{14}$
Paclitaxel is 5β, 20 - Epoxy - 1, 2α, 4, 7β, 10β, 13α - hexahydroxytax - 11 - en - 9 - one 4, 10 - diacetate 2 - benzoate 13 - ester with (2R, 3S) - N - benzoyl - 3 - phenylisoserine.

Paclitaxel is white to off white crystalline powder. It is highly lipophilic, insoluble in water and melts at around 213-217 ^{O}C.

COMPOSITION

Each ml contains:	
Paclitaxel IP	6 mg
Polyoxyl 35 castor oil U.S.N.F	527 mg
Dehydrated Alcohol IP	49.7 % (v/v)

CLINICAL PHARMACOLOGY

Mode of Action
Paclitaxel exerts its effect on microtubules and their protein subunits. It acts on microtubules by preventing depolymerization. Paclitaxel exposure results in blockade of the cell cycle in G2 or M phase. Other potential mechanisms of cytotoxicity include inhibition of DNA synthesis and/or inhibition of cell migration. In addition, Paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple assets of microtubules during mitosis.

PHARMACOKINETICS

Distribution
Distribution Sites
Protein Binding: 89-98 %
Other distribution sites
Cerebrospinal fluid: 2.74 µmol/L
Distribution Kinetics
Volume of Distribution - 67 to 182 L/m^2.

Metabolism
Sites and Kinetics

LIVER, extensive - Paclitaxel is metabolized by the cytochrome P450 isozymes CYP2C8 and CYP3A4. Recovery of paclitaxel in the feces accounted for 5 % of an administered dose while the total recovery of paclitaxel and metabolites in feces accounted for 56 - 101 % of an administered dose.

Metabolites

6 alpha - hydroxypaclitaxel (inactive)

3' - p - hydroxypaclitaxel (inactive)

6 alpha - 3' - p - hydroxypaclitaxel (inactive)

Excretion

Kidney (Renal Excretion) - 1.3 - 12.6 %.

Total Body Clearance - 12.2 - 23.8 liters/hour/square meter.

Other Excretion - Bile, extensive - High concentrations of paclitaxel (and an unidentified metabolite) was observed in the bile of patients with biliary catheters. Elimination half-life Parent Compound : 13.1 - 52.7 hours

DOSAGE AND ADMINISTRATION

PACLIWEL® should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents. All patients must be pre-medicated with corticosteroids, antihistamines and H2 antagonists prior to Paclitaxel. The following is a recommended premedication regimen: dexamethasone (8 - 20 mg) given orally (12 and 6 hours) or intravenously (30 - 60 mins) prior to Paclitaxel , chlorpheniramine 10 mg intravenously or an equivalent antihistamine (30 - 60 mins) before Paclitaxel and cimetidine (300 mg) or ranitidine (50 mg) intravenously (30 - 60 mins) before Paclitaxel. Appropriate supportive medications should be readily available in case of severe hypersensitivity reactions. Paclitaxel should be administered via infusion control device (pump) using non-PVC tubing and connectors. An in-line filter with a microporous membrane not greater than 0.22 µm should be attached to the intravenous tubing during infusion of for use of cisplatin in treatment of advanced ovarian carcinoma and non-small cell lung carcinoma.

For previously untreated patients with carcinoma of the ovary, the following regimens may be given every 3 weeks:

a. PACLIWEL® administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or

b. PACLIWEL® administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.

For patients with carcinoma of the breast, the following regimen is recommended:

For the adjuvant treatment of node-positive breast cancer, the recommended regimen is PACLIWEL®, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for four courses administered sequentially to doxorubicin containing combination chemotherapy.

For patients with non-small cell lung carcinoma, the following regimen is recommended:

Every 3 weeks, PACLIWEL® should be administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with AIDS-related Kaposi's sarcoma:

PACLIWEL® is 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 (dose intensity 45 to 50 mg/m^2/week).

For the therapy of patients with solid tumors (ovary, breast, and NSCLC):

Courses of PACLIWEL® 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.

Hepatic Impairment: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III to IV myelosuppression dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

INDICATION

PACLIWEL® is indicated as first line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first line therapy, paclitaxel is indicated in combination with cisplatin.

PACLIWEL® is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin containing combination chemotherapy.

PACLIWEL® in combination with cisplatin is indicated for the first line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and or radiation therapy.

PACLIWEL® is indicated for the second line treatment of AIDS related Kaposi's sarcoma.

CONTRAINDICATIONS

PACLIWEL® is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated on polyoxyethylated castor oil.

PACLIWEL® should not be used in patients with solid tumors who have baseline neutrophil counts <1500 cells/mm^3 or in patients with AIDS related Kaposi's sarcoma with baseline neutrophil counts <1000 cells/mm^3.

ADVERSE EFFECTS

Body as a whole: Hypersensitivity reaction, anaphylaxis and anaphylactic shock, angioedema, ataxia, sepsis, chills and fever, asthenia, fever, rigor, headache, paresis, chest pain, fatigue, infusion-related symptoms, peripheral oedema, bone pain, coma, meningitis, cerebral oedema, thinking abnormal, progression of neoplasia.

Digestive: Hepatocellular damage, liver tenderness, diarrhoea, nausea and vomiting, pancreatitis, hepatic failure, jaundice.

Cardiovascular: Cardiomyopathy, congestive heart failure, increased congestive heart failure, decreased ejection fraction, hypotension, pericardial effusion, bradycardia, cerebrovascular disorder, cardiac failure, cardiogenic shock, pericarditis.

Blood and Lymphatic: Leukaemia, febrile neutropenia, neutropenia, thrombocytopenia, anaemia, hypoprothrombinemia

Infections: Cellulitis, erysipelas.

Metabolic: Hyperkalaemia

Musculoskeletal: Myalgia

Nervous: Paraneoplastic cerebellar degeneration

Renal: Membranous glomerulonephritis, glomerulonephropathy, renal failure.

Respiratory: Bronchospasm, respiratory distress, acute pulmonary oedema, respiratory insufficiency, dyspnoea, hypoxia, laryngeal oedema, acute respiratory distress, acute respiratory distress syndrome, Cheyne-Stokes breathing, pulmonary infiltrates, pneumonia, pneumonitis, pulmonary fibrosis.

Skin and Appendages: Rash, dermatitis, urticaria, Stevens-Johnson syndrome.

Other clinical effects: Alopecia, edema, and nail color changes observed in few patients.

WARNINGS

PACLIWEL® should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 - 4 % of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. 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 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.

USE IN PREGNANCY AND LACTATION

Paclitaxel cause fatal harm when administered to a pregnant woman. Paclitaxel at an intravenous dose of 0.6 mg/kg/day produced reproductive and foetal developmental toxicity in rats. Paclitaxel is contraindicated for use in pregnancy. Women should be advised to use effective means of contraception to avoid becoming pregnant during therapy with Paclitaxel and to inform the treating physician immediately should this occur. Paclitaxel is contraindicated during lactation. It is unknown whether paclitaxel is excreted in human milk. Therefore, breast-feeding should be discontinued for the duration of paclitaxel therapy.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. 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 paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

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

Hypersensitivity reactions: Patients with a history of severe hyper - sensitivity reactions to products containing polyoxyethylated castor oil (eg, cyclosporine for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_1 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. Patients who have developed severe hyper - sensitivity reactions should not be rechallenged with paclitaxel.

Cardiovascular: Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended.

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 paclitaxel.