Paclitaxel

Paclib®

6 mg/mL (30 mg/5 mL)
6 mg/mL (100 mg/16.67 mL)
Concentrate Solution for Intravenous Infusion
Antineoplastic

FORMULATION
Each mL solution for intravenous infusion contains:
Paclitaxel ……..…….. 6 mg

PRODUCT DESCRIPTION
Paclitaxel concentrated solution for intravenous infusion is a limpid yellowish viscous liquid, free from suspended particles.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS / MECHANISM OF ACTION
Paclitaxel is a member of the taxane group of anticancer drugs. It is a potent inhibitor of tumor cell replication, blocking cells in the late G2 to M phase of the cell cycle. Paclitaxel promotes abnormal assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability disrupts the normal dynamic reorganization of the microtubule network which is essential for mitosis/cell replication. Paclitaxel also induces abnormal arrays of microtubules throughout the cell cycle and multiple esters of microtubules during mitosis, further disrupting cell function.

PHARMACOKINETICS
Paclitaxel exhibits nonlinear, dose-dependent pharmacokinetics, especially when the drug is administered over short infusion periods (e.g., 3 hours). Relatively small changes in dose may lead to large changes in peak plasma concentrations and total drug exposure due to the nonlinearity of paclitaxel's pharmacokinetics. Paclitaxel's peak plasma concentration and area under the curve (AUC) exhibit interindividual variation after intravenous (IV) administration. Peak plasma concentrations increase during continuous IV administration of paclitaxel and decline immediately after infusion.

Paclitaxel is widely distributed in body fluids and tissues. The dose and duration of infusion affect paclitaxel's volume of distribution. After a 24-hour infusion, the mean apparent volume of distribution at steady state ranged from 227 to 688 L/m^2 in patients with advanced ovarian cancer. The steady-state volume of distribution ranged from 18.9 to 260 L/m^2 at a dose of 200 to 500 mg/m^2 in children with solid tumors or refractory leukemia. Approximately 88 to 98% of paclitaxel is protein-bound. It is detected in the ascitic fluid after IV infusion and does not readily penetrate the CNS.

Plasma concentrations of paclitaxel fall in a biphasic manner with a distribution half-life of 0.34 hour. Average elimination half-life is 5.8 hours in adults with malignancy after 6 to 24 hours IV infusion. After a 3-hour IV infusion of 175 mg/m^2, the average distribution half-life and elimination half-life is 0.27 hour and 2.33 hours, respectively. Paclitaxel is metabolized extensively in the liver by cytochrome P450 (CYP3A4 may play a minor role) to its major metabolite, 6α-hydroxypaclitaxel. It is excreted principally in the feces via biliary excretion. Less than 10% of the administered dose is excreted in the urine. Paclitaxel's clearance is decreased by almost 25 to 33% when paclitaxel is administered after cisplatin.

Paclitaxel is minimally removed by hemodialysis.

INDICATIONS
Ovarian Cancer
- First-line treatment of advanced ovarian cancer in combination with cisplatin
- Subsequent treatment of advanced ovarian cancer

Breast Cancer
- Adjuvant treatment of node positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.
- Treatment of breast cancer after the failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- For the initial treatment of locally advanced or metastatic breast cancer:
  - In combination with an anthracycline in patients for whom anthracycline therapy is suitable, **OR**
  - In combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom anthracycline is not suitable.

Advanced Non-small Cell Lung Cancer (NSCLC)
- First-line treatment, in combination with cisplatin, of patients with NSCLC who are not candidates for surgery and/or radiation therapy;

AIDS-related Kaposi's Sarcoma
- Palliative treatment of advanced or refractory AIDS-related Kaposi's sarcoma in patients who have failed prior liposomal anthracycline therapy.

DOSAGE AND ADMINISTRATION
Premedication Regimen
Premedicate all patients with oral dexamethasone (20 mg) approximately 12 and 6 hours before paclitaxel administration, IV diphenhydramine or its equivalent (50 mg) 30 to 60 minutes before paclitaxel, and either IV cimetidine (300 mg) or IV ranitidine (50 mg) 30 to 60 minutes before paclitaxel in order to reduce the incidence of hypersensitivity reactions.
Patients with HIV infection may follow the same premedication regimen with the exception of a reduced dose of oral dexamethasone (10 mg).

Paclitaxel Injection must be diluted prior to intravenous infusion.

Indications	Recommended Paclitaxel Intravenous (IV) Infusion Regimen
Ovarian Cancer	**Previously untreated patients with ovarian cancer:** Paclitaxel 175 mg/m^2 administered IV over 3 hours followed by cisplatin 75 mg/m^2; may be given every 3 weeks, **OR** Paclitaxel 135 mg/m^2 administered IV over 24 hours followed by cisplatin 75 mg/m^2; may be given every 3 weeks.
	Previously chemotherapy-treated ovarian cancer patients: Paclitaxel 135 or 175 mg/m^2 administered IV over 3 hours; given every 3 weeks.
Breast Cancer	**Adjuvant treatment of node positive breast cancer:** Paclitaxel 175 mg/m^2 administered IV over 3 hours given every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy.
	After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy: Paclitaxel 175 mg/m^2 administered IV over 3 hours given every 3 weeks.
	For HER-2 overexpressing breast cancer: Paclitaxel 175 mg/m^2 administered IV over 3 hours; given every 3 weeks for 6 cycles. Administer trastuzumab 2 mg/kg IV once a week until progression of disease after an initial loading dose of 4 mg/kg body weight.
Non-small Cell Lung Cancer (NSCLC)	Paclitaxel 135 mg/m^2 administered IV over 24 hours followed by cisplatin 75 mg/m^2, given every 3 weeks, **OR** Paclitaxel 175 mg/m^2 administered IV over 3 hours followed by cisplatin 80 mg/m^2, given every 3 weeks.
AIDS - Related Kaposi's Sarcoma	Paclitaxel 135 mg/m^2 administered IV over 3 hours given every 3 weeks, **OR** Paclitaxel 100 mg/m^2 administered IV over 3 hours given every 2 weeks (dose intensity 45-50 mg/m^2 per week) • In clinical trials, all patients with low performance status were treated with 100 mg/m^2 every 2 weeks; paclitaxel 135 mg/m^2 every 3 weeks was shown to be more toxic.
	Or, as prescribed by a physician

General Dosing Information
- Monitor vital signs regularly, particularly during the first hour of administration. Cardiac monitoring is not required except in patients with preexisting cardiac abnormalities.
- Closely monitor the infusion site for possible infiltration during drug administration particularly during longer periods of infusion (e.g., 24 hours). Local reactions may appear 7 to 10 days after completion of paclitaxel infusion.

Dose Adjustments
- For patients with solid tumors (ovary, breast, NSCLC): Paclitaxel courses should not be repeated until the patient's neutrophil count is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.
- Reduce dose by 20% for subsequent courses of paclitaxel in patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during paclitaxel therapy.
- For AIDS-related Kaposi's Sarcoma:
  - Initiate or repeat treatment only if the neutrophil count is at least 1000 cells/mm^3.
  - Reduce dose by 20% for subsequent courses of paclitaxel in patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer)
  - Initiate concomitant hematopoietic growth factor (G-CSF) as clinically needed.
- Dosing in Patients with Hepatic Impairment:

Degree of Hepatic Impairment*			Recommended Dose
Transaminase Levels		Bilirubin Levels	
24 - hour Infusion			
< 2 x ULN	and	≤ 1.5 mg/dL	135 mg/m^2
2 to < 10 x ULN	and	≤ 1.5 mg/dL	100 mg/m^2
< 10 x ULN	and	1.6 to 7.5 mg/dL	50 mg/m^2
≥ 10 x ULN	or	> 7.5 mg/dL	NOT RECOMMENDED
3 - hour Infusion			
< 10 x ULN	and	≤ 1.25 x ULN	175 mg/m^2
< 10 x ULN	and	1.26 to 2 x ULN	135 mg/m^2
< 10 x ULN	and	2.01 to 5 x ULN	90 mg/m^2
≥ 10 x ULN	or	> 5 x ULN	NOT RECOMMENDED

* These recommendations are based on dosages of 135 mg/m^2 over 24 hours and 175 mg/m^2 over 3 hours for patients without hepatic impairment; these are not applicable to patients with Kaposi's Sarcoma.

Preparation for Intravenous Infusion
Paclitaxel for injection must be diluted prior to use for IV infusion to produce a solution containing 0.3 to 1.2 mg of paclitaxel per mL. Compatible solutions are as follows: 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, and 5% dextrose in Ringer's injection.

Visually inspect paclitaxel solution for particulate matter or discoloration prior to use. The resulting solution may show turbidity caused by the preparation solvent.

Administer through an in-line filter with a microporous membrane not greater than 0.22 micron.

Stability after reconstitution
Paclitaxel solution, when diluted as recommended, is stable for 24 hours at temperatures between 15° to 30° C.

Incompatibilities:
Undiluted paclitaxel should not come in contact with plasticized polyvinyl chloride (PVC) equipment or devices. Paclitaxel should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-covered administration sets to avoid leaching from PVC infusion bags or sets.

Paclitaxel solutions are reported to be physically incompatible with the following drugs: amphotericin B, chlorpromazine hydrochloride, hydroxyzine hydrochloride, methylprednisolone, sodium succinate, and mitoxantrone hydrochloride.

Handling and Disposal Precautions
- Use protective gloves when handling paclitaxel solution for injection since skin reactions (e.g., tingling, burning, erythema) may occur with accidental exposure to the drug.
- Wash the affected area immediately and thoroughly with soap and water if paclitaxel comes in contact with skin / mucous membrane.
- Avoid inhalation during preparation and administration of paclitaxel solutions. Inhalation may cause dyspnea, chest pain, burning eyes, sore throat, and nausea.

CONTRAINDICATIONS
- Hypersensitivity to paclitaxel, Cremophor EL (polyoxyethylated castor oil), or any component of the product.
- Since the product contains ethyl alcohol as an excipient, it should not be administered to pregnant women, children, and patients with hepatic dysfunction, alcoholism and epilepsy.
- Patients with solid tumors who have baseline neutrophil count of less than 1500 cells/mm^3
- Patients with AIDS-related Kaposi's sarcoma who have baseline neutrophil counts of less than 1000 cells/mm^3 and those with concurrent, serious, uncontrolled infections.

WARNINGS AND PRECAUTIONS
- 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 2 to 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 H_2-antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should discontinue infusion immediately and should not be rechallenged with the drug.
- Paclitaxel therapy should not be administered to patients with solid tumors who have baseline neutrophil counts below 1500 cells/mm^3 and should not be administered to patients with AIDS-related Kaposi's sarcoma if baseline neutrophil count is below 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 (See **Contraindications**).

General: Paclitaxel has a low therapeutic index. Therapeutic response is not likely to occur without evidence of toxicity.

Cardiovascular: Hypotension, hypertension and bradycradia have been reported but patients are usually asymptomatic and generally do not require treatment. Severe cases of conduction abnormalities have been reported in <1% of patients receiving paclitaxel. In severe cases, paclitaxel infusions may need to be interrupted or discontinued at the discretion of the physician. Cardiac function monitoring is recommended in patients with preexisting cardiac abnormalities and when paclitaxel is co-administered with doxorubicin in patients with metastatic breast cancer.
If patients develop significant cardiac function abnormalities during administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with paclitaxel.

Hepatic: Patients with hepatic impairment may be at an increased risk of toxicity mainly grade III to IV myelosuppression. Increased myelosuppression may be observed in patients with moderate to severe hepatic impairment. Paclitaxel is not recommended in patients with severely impaired hepatic function (transaminase levels ≥ 10 x ULN or bilirubin levels > 7.5 mg/dL or > 5 x ULN; see **Dosage and Administration**).

Neurologic: Peripheral neuropathy (dose-dependent) may occur frequently. Carefully monitor patient with pre-existing peripheral neuropathy and in severe cases, reduce all subsequent doses by 20% (see **Dosage and Administration**).

Hypersensitivity: Patients with a history of severe hypersensitivity reaction to products containing Cremophor EL should not be treated with paclitaxel (see **Contraindications**). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, immediate discontinuation of paclitaxel and aggressive symptomatic therapy should be done in cases of severe reactions such as hypotension requiring treatment dyspnea requiring bronchodilators, angioedema or generalized urticaria.

Injection Site Reaction: Erythema, tenderness, skin discoloration, or swelling at the injection site may occur. Recurrence of skin reactions at a previous site of extravasation (i.e., "recall" reactions) after paclitaxel administration at a different injection site has been reported rarely. More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have also been reported rarely (see **Dosage and Administration**).

Gastrointestinal: Exclude bowel perforation in patients receiving paclitaxel who complain of abdominal pain with other signs and symptoms.

Infectious Complications: Patients should be informed to take extra precautions to reduce the risk of infection or bleeding (e.g., avoiding people with infection, getting cut or bruised)

The risk-benefit should be considered when administering paclitaxel to patients with the following conditions:
- Varicella or recent exposure to such disease
- Herpes Zoster
- Infection
- Precaution must be taken in patients who have undergone therapies with cytotoxic drugs, including radiotherapy

CARCINOGENICITY, MUTAGENICITY, FERTILITY
There is no study on the carcinogenic potential of paclitaxel. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice) mammalian test system but was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.
Reproduction studies in rats and rabbits showed evidence of maternal toxicity, embryotoxicity and fetotoxicity during organogenesis at IV doses of 1 mg/kg (6 mg/m^2 or systemic exposures approximately equivalent to 0.04 times the maximum recommended human dose on a mg/m^2 basis) and 3 mg/kg (33 mg/m^2 or systemic exposures approximately equivalent to 0.2 times the maximum recommended human dose on a mg/m^2 basis), respectively. These resulted in intrauterine mortality, increased resorptions, increased fetal deaths and reduced fertility.
Paclitaxel produced low fertility in rats at an IV dose of 1 mg/kg (6 mg/m^2).

EFFECTS ON THE ABILITY TO DRIVE OR USE MACHINES
The alcohol content in the product may impair the ability to perform hazardous activities requiring mental alertness following paclitaxel infusion, particularly when high doses of the drug are administered over short periods (e.g., 3 hours). Concomitant use with CNS depressants should be done with caution.

INTERACTIONS WITH OTHER MEDICAMENTS
Antineoplastic Agents: Administration of paclitaxel with other antineoplastic agents showed sequence-dependent interactions and may affect their toxicities.
- It is recommended that paclitaxel be administered before cisplatin to decrease the risk of increased severity of myelosuppression.
- When cyclophosphamide is administered after paclitaxel (by 24-hour IV infusion), the severity of neutropenia and thrombocytopenia has been reported to increase.
- Plasma levels of doxorubicin and its active metabolite doxorubicinol may be increased when paclitaxel and doxorubicin are used concomitantly. Paclitaxel should be administered 24 hours after doxorubicin.
- Fluorouracil pretreatment was reported to inhibit the action of paclitaxel.

Myelosuppressive Agents: The combination of paclitaxel with other myelosuppressive agents may increase the severity of myelosuppression depending on the dose.

Similar rates of neutropenia but less severe thrombocytopenia was reported when carboplatin is administered after paclitaxel compared with carboplatin administered alone.

Blood Dyscrasia: The combination of paclitaxel with these drugs can cause blood dyscrasia, usually in a minority of patients, and not dose-related: aminopyrine, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, tricyclic antidepressants, oral antidiabetic agents, non-steroidal anti-inflammatory drugs (NSAIDs), carbamazepine, chloramphenicol, clozapine, dapsone, foscarnet, levamisole, penicillamine, phenothiazine, primaquine, primidone, procainamide, propafenone, rifampicin, sulfonamides, thioxanthenes, trimethoprim, valproate, and valproic acid.

Drugs Affecting Hepatic Enzymes: Concomitant use of drugs which induce or inhibit the action of cytochrome P-450 isoenzymes may reduce or increase the plasma concentrations of paclitaxel, respectively.
Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (e.g., ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated.
Ketoconazole may inhibit the metabolism of paclitaxel when given together.

CNS Depressants: CNS depression due to the alcohol content of the formulation may be potentiated when paclitaxel and CNS depressants such as antihistamines or opiates are used together.

Vaccines: Paclitaxel may cause immunosuppression. The interval between the discontinuation of paclitaxel and the patient's capacity to respond to the vaccine depends on the type and intensity of immunosuppression. The estimated time is between 3 months and 1 year.

Immunization with oral poliovirus vaccine must be postponed in people who are in close contact with patients undergoing paclitaxel therapy, especially family members.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

PREGNANCY AND LACTATION
Pregnancy Category D
Paclitaxel can cause fetal harm when administered to pregnant women. Women who are pregnant or those wanting to become pregnant should be advised to avoid becoming pregnant during paclitaxel therapy. Paclitaxel should be used only when clearly needed and when potential benefits outweigh the unknown hazards to the baby.

Breastfeeding: It is not known whether paclitaxel is distributed to human milk. Breastfeeding is not recommended during chemotherapy because of the potential serious adverse reactions to paclitaxel by the breastfeeding infant.

GERIATRICS
The safety and efficacy of paclitaxel in elderly patients have not been clearly established. However, most of the patients treated for refractory metastatic ovarian carcinoma are older than 60 years. There is no evidence of age-related differences in the safety or dose tolerance between young and old patients. However, clinical studies show that severe myelosuppression, severe neuropathy and cardiovascular events were more frequent in elderly patients. Estimates of efficacy appeared similar between elderly and younger patients but comparative efficacy could not be determined due to a small number of elderly patients studied.

CHILDREN
The safety and efficacy of paclitaxel in children have not been established. In a clinical trial in children, high dose paclitaxel (350 to 420 mg/m^2 or more than two times the recommended dose) infused over 3 hours caused CNS toxicity (rarely associated with death). The toxicity is attributed to the high dose alcohol content (vehicle) given over a short infusion time. Concomitant use of antihistamines may intensify this effect.

HEPATIC AND RENAL IMPAIRMENT
The use of paclitaxel in patients with impaired renal and hepatic function has not been fully established. Since paclitaxel is metabolized in the liver, dose reduction is recommended in patients with moderate to severe liver failure. Dose reduction may not be necessary in patients with renal failure. (See **Dosage and Administration**)

ADVERSE EFFECTS / UNDESIRABLE EFFECTS
Hematologic Effects: Bone marrow suppression is the major and dose-limiting adverse effect. Dose-related myelosuppression is manifested mainly by leukopenia, thrombocytopenia and anemia. The frequency and severity of hematologic toxicity increase with dose, especially at paclitaxel doses exceeding 190 mg/m^2. Eosinophilia was reported in patients with AIDS-related Kaposi's sarcoma. Few reports of severe hemorrhage were also attributed to paclitaxel.
Dose- and schedule- dependent paclitaxel-induced neutropenia is generally rapidly reversible. The onset of neutropenia usually occurs 8 to 10 days and neutrophil nadirs generally occur at a median of 10 to 12 days after paclitaxel administration. Neutrophil counts commonly recover 15 to 21 days after administration.
Febrile neutropenia associated with infectious episode, including urinary tract infection (UTI) and upper respiratory tract infection (URTI) have been commonly reported.
Acute myeloid leukemia and myelodysplastic syndrome are very rare.

Infectious Complications: Fever was associated with 12% of all paclitaxel courses (as single agent) in patients with solid tumors. Most frequently reported were urinary and respiratory tract infections. Infectious complications, including sepsis, pneumonia and peritonitis were also reported. Infectious episodes were fatal in 1% of all patients.

Hypersensitivity Reactions: Flushing, rash, skin reactions, dyspnea, hypotension, tachycardia, hypertension, chest pains, angioedema, and generalized urticaria. Abdominal pain, pain in the extremities, diaphoresis, cutaneous reactions (e.g., acral erythema, generalized pustular dermatosis, and bullous fixed drug eruption) have also been reported. Chills, shock, and back pain associated with hypersensitivity to paclitaxel have been rarely reported (see **Warnings and Precautions**).

Cardiovascular Effects: Hypotension and bradycardia are the most common cardiovascular adverse effects of paclitaxel. These are generally asymptomatic and do not require treatment.
ECG abnormalities including nonspecific repolarization, sinus bradycardia, sinus tachycardia, and premature beats were seen in paclitaxel-treated patients.
Chest pain and hypertension are often associated with hypersensitivity reactions.
Severe cardiovascular effects include arrhythmia (e.g., asymptomatic ventricular tachycardia, bigeminy, atrial fibrillation, supraventricular tachycardia, junctional tachycardia), syncope, hypertension, venous thrombosis, and severe conduction abnormalities. Cerebrovascular infarction, vascular toxicity, including myocardial infarction have been reported rarely; AV block has also been reported.
Congestive heart failure and cardiomyopathy associated with acute renal failure have been reported; edema has also been reported.

Nervous System Effects: Peripheral neuropathy manifested as mild paresthesia with numbness and tingling in a stocking-glove distribution have been reported. Burning pain (often associated with hyperesthesia), particularly in the feet, and perioral numbness have also been reported.
Seizures (including tonoclonic seizures), syncope, ataxia, and neuroencephalopathy have occurred rarely during or immediately after administration of paclitaxel. Convulsions, dizziness, headache, and autonomic neuropathy resulting in paralytic ileus have also been reported rarely.

Musculoskeletal Effects: Arthralgia and/or myalgia consisting of pain in the large joints of the arms and legs have been reported. Gabapentin may be beneficial for the management of these conditions.

Gastrointestinal (GI) Effects: Nausea and vomiting, diarrhea, anorexia, taste perversion, mucositis characterized by diffuse ulceration of the lips, oral cavity and pharynx have been reported. Dysphagia and pain reflecting esophageal involvement may also occur. Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been reported. Neutropenic enterocolitis (typhlitis) has been observed despite co-administration of G-CSF.
Adverse GI effects of paclitaxel are generally mild to moderate in severity at current recommended doses.

Dermatologic Effects: Patients receiving paclitaxel may experience reversible alopecia, loss of all body hair including axillary, pubic and extremity hair, eyelashes, and eyebrows. Transient skin changes, nail changes (changes in pigmentation, discoloration of nail bed), radiation recall dermatitis resulting in extensive desquamation and necrosis, and maculopapular rash may occur. Pruritus was reported in patients receiving high-dose paclitaxel.

Hepatic Effects: Abnormalities in liver function test results have occurred; increased serum alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin concentrations have been reported in patients with normal baseline hepatic function. Cumulative hepatic toxicity has been associated with prolonged exposure to paclitaxel. Hepatic necrosis and hepatic encephalopathy resulting in death have occurred rarely. Fatal hepatic coma has also occurred.

A higher trend of elevated liver function test was observed in patients with Kaposi's Sarcoma compared to patients with solid tumors.

Renal Effects: Renal toxicity including acute renal failure and reversible increases in serum creatinine levels have been reported. Patients with Kaposi's Sarcoma and patients treated with paclitaxel and cisplatin have a higher risk of developing renal toxicity or renal failure.

I**njection Site Reaction** (see **Warnings and Precaution**s)

Respiratory Effects: Rare reports of interstitial pneumonia, lung fibrosis, pulmonary embolism, pleural effusion, and respiratory failure. Paclitaxel together with radiation therapy may cause radiation pneumonitis and interstitial pneumonia. Transient pulmonary infiltrates has also been reported.

Ocular Effects: High dose paclitaxel may result in loss of visual acuity. Abnormalities observed in visual evoked potentials in some patients suggest persistent damage of the optic nerve. Other visual problems encountered include scintillating scotomata and photopsia which appear to be reversible.

Otic Effects: Ototoxicity (e.g., hearing loss, tinnitus and vertigo) has been reported in patients receiving paclitaxel but very rarely.

Accidental Exposure:
- **Inhalation:** Dyspnea, chest pain, burning eyes, sore throat and nausea.
- **Topical:** Tingling, burning and redness.

Others: Asthenia and malaise.

OVERDOSAGE AND MANAGEMENT
Primary anticipated complications of paclitaxel overdosage consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Pediatric overdose may be attributed to the alcohol content of the formulation. There is no known antidote for paclitaxel overdosage. Treatment is symptomatic and supportive. Discontinue paclitaxel and initiate appropriate supportive measures for the type of toxicity observed. Only a minimal portion of paclitaxel is removed by hemodialysis.

AVAILABILITY
Type 1 colorless vial in 5 mL and 16.67 mL (Box of 1 vial).

STORAGE CONDITION
Store in a refrigerator at 2°C to 8°C. Protect from light.
Freezing does not adversely affect the product.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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