TAJ PHARMA

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Rx Paclitaxel 6mg/mL
Injection USP Sterile· Multi-Dose Vial
For Intravenous Infusion after dilution
•30mg/ •100mg / •150mg / •250mg/•260mg/ •300mg

PACLITAXEL INJECTION USP
30mg/ 100mg / 150mg / 250 mg/ 260 mg/ 300 mg

Rx only

COMPOSITION

Paclitaxel 30

Paclitaxel injection USP 30 mg/5 ml Each ml contains		
Paclitaxel USP		6.0 mg
Polyoxyl 35 Castor oil USNF	527 mg	
Dehydrated alcohol USP	49.7% v/v	

Paclitaxel 100

Paclitaxel injection USP 100 mg/16.7 ml Each ml contains		
Paclitaxel USP		6.0mg
Polyoxyl 35 Castor oil USNF	527mg	
Dehydrated alcohol USP	49.7% v/v	

Paclitaxel 150

Paclitaxel injection USP 150 mg/25 ml Each ml contains		
Paclitaxel USP		6.0mg
Polyoxyl 35 Castor oil USNF	527mg	
Dehydrated alcohol USP	49.7% v/v	

Paclitaxel 250

Paclitaxel injection USP 250 mg/41.7 ml Each ml contains		
Paclitaxel USP		6.0mg
Polyoxyl 35 Castor oil USNF	527mg	
Dehydrated alcohol USP	49.7% v/v	

Paclitaxel 250

Paclitaxel injection USP 260 mg/43.3 ml Each ml contains		
Paclitaxel USP		6.0mg
Polyoxyl 35 Castor oil USNF	527mg	
Dehydrated alcohol USP	49.7% v/v	

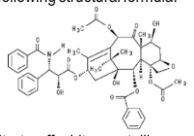
Paclitaxel 300

Paclitaxel injection USP 300 mg/50.0 ml Each ml contains		
Paclitaxel USP		6.0mg
Polyoxyl 35 Castor oil USNF	527mg	
Dehydrated alcohol USP	49.7% v/v	

DESCRIPTION

Paclitaxel (paclitaxel) injection is a clear colorless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. **Paclitaxel** is available in 30mg (5ml), 100mg (16.7ml), and 300mg (50mL) Multidose vials. Each mL of sterile non-pyrogenic solution contains 6 mg pactitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Paclitaxel is a natural product with antitumor activity. **Paclitaxel** is obtained via a semi-synthetic process from Taxus baccata. The chemical name for paclitaxel is 5B, 20-Epoxy-1, 2a, 4, 7B, 10B, 13a-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13-ester with (2 R, 3S)-N-benzoyl-3phenylisoserine.
Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimmers 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 **Paclitaxel,** paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.
Pharmacokinetics parameters of paclitaxel following 3-and 24-hour infusions of **Paclitaxel** at dose levels of 135 and 175mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer anemia (Hb<11 g/dl) was observed in 78% of all patients and was severe (Hb < 8g /dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed in patients. It appeared that with the 24-hour infusion of **Paclitaxel,** a 30% increase in Dose (135 mg/m^2 versus 175 mg/m^2) increased the Cmax by 87%, whereas the AUC **(o-¥)** remained proportional. However, with a 3-hour infusion, for a 30% increase in dose (135 MG/M^2 VERSUS 175MG/M^2) increased the Cmax by 87%, whereas the AUC remained proportional. However, with a 3-hour infusion, for a 30% increase in dose, the Cmax and AUC (0-¥) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24-hour infusion of **Paclitaxel,** ranged from 227 to 688 L/m^2, indicating extensive extra vascular distribution and/or tissue binding of paclitaxel.
The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15-135 mg/m^2 given by 6-hour infusions (n=36), and 200-275 mg/m^2 given by 24-hour infusions (n=54) in phase 1 & 2 studies.

INDICATIONS & USAGE

Paclitaxel 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.
Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequently to standard doxorubicin-containing combination chemotherapy. **Paclitaxel** is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthrax-cycline unless clinically contraindicated.
Paclitaxel, 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.
Paclitaxel is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

CONTRAINDICATIONS

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to **Paclitaxel** or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).
Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of. <1500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in2%-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.
Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity, **Paclitaxel** should not be administered. To patients with baseline neutrophil counts of less than 1500 cells/mm^3 (<1000 cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be instituted during **Paclitaxel** treatment. Patients should not be retreated with subsequent cycles of **Paclitaxel** until neutrophils recover to a level> 1500 cells/mm^3 (> 1000 cells/mm^3 for patients with KS) and platelets recover to a level > 100,000 cells/mm^3. If patients develop significant conduction abnormalities during **Paclitaxel** infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with **Paclitaxel.**

PRECAUTIONS

Pregnancy Category D.
Paclitaxel can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If **Paclitaxel** (paclitaxel) Injection 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 fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

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/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo-and fetotoxicity.

Nursing Mothers

It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel Injection to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. 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 **Paclitaxel** therapy.

Pediatric Use

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

Geriatric Use

Of 2228 patients who received **Paclitaxel** in eight clinical studies evaluation its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive **Paclitaxel** in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with **Paclitaxel** had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients.

Hepatic Impairment

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

Adverse Reactions

Hematologic

Bone marrow suppression was the major dose-limiting toxicity of Paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3-hour infusion, neutrophil counts declined below 500 cells/mm3 in 14% of the patients treated with a dose of 135 mg/m2 compared to 27% at a dose of 175 mg/m2 (p=0.05). In the same study, severe neutropenia (<500 cells/mm3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Fever is frequent. Episodes of sepsis, pneumonia, peritonitis & UTI and upper respiratory tract infections were the most frequently reported infectious complications. The use of supportive therapy, including G-CSF, s

recommended for patients who have experienced severe neutropenia. Thrombocytopenia is uncommon, and almost never severe (<50,000 cells/mm^3). Anemia (Hb <11 g/dL) is observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia is observed.

Hypersensitivity Reactions (HSRs)

The frequency and severity of HSRs were not affected by the dose or schedule of **Paclitaxel** administration. No severe reactions were observed. Severe symptoms occurred generally within the first hour of **Paclitaxel** infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain, and tachycardia.
The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), and hypertension (1%). 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 part of the continuing surveillance of **Paclitaxel** safety.

Respiratory

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

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. These reactions have been observed more frequently with the 24-hour infusion than with the 3- hour infusion.

DRUG INTERACTIONS

Using escalating doses of **Paclitaxel** (110-200 mg/m^2) and Cisplatin (50 or 75 mg/m^2) given as sequential infusions. Melosuppression was more profound when **Paclitaxel** was given after Cisplatin than with the alternate sequence (i.e., **Paclitaxel** before Cisplatin). The metabolism of **Paclitaxel** is catalyzed by cytochrmome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering **Paclitaxel** concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Plasma levels of doxorubicin (and its active metabolite doxorubicin) may be increased when paclitaxel and doxorubicin are used in combination.

DOSAGE AND ADMINISTRATION

All patients should be premeditated prior to **Paclitaxel** administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before **Paclitaxel,** diphenhydramine (or its equivalent) 50mg IV 30 to 60 minutes prior to **Paclitaxel,** and Cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before **Paclitaxel.**
1) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered.
a) **Paclitaxel** 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) **Paclitaxel** administered intravenously over 24 hours at a dose of 135mg/m^2 followed by Cisplatin at a dose of 75mg/m^2.
2) In patients previously treated with chemotherapy for carcinoma of the ovary, **Paclitaxel** (paclitaxel) Injection has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is **Paclitaxel** 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours, every 3 weeks.
3) For patients with carcinoma of the breast, the following regimens are recommended.
a) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is **Paclitaxel,** 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. The clinical trial used four courses of doxorubicin and cyclophosphamide.
b) After failure of initial chemotherapy for metastatic disease or replase within 6 months of adjuvant chemotherapy. Paclitaxel at a dose of 175 mg/m2 administered intravenously over 3 hours, every 3 weeks has been shown to be effective. For patients with non-small cell lung carcinoma, the recommended regimen, given every 3 weeks, is **Paclitaxel** administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by Cisplatin, 75mg/m^2.
4) For patients with AIDS-related Kaposi's sarcoma, **Paclitaxel** 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 45-50 mg/m^2/week). In the two clinical trials evaluating these schedules these schedules, the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2, every 2 weeks).
For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of **Paclitaxel** 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. **Paclitaxel** should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/ mm^3 and the platelet count is at least 100,000 cells/mm^3. **Paclitaxel** should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm^3. Patients who experience severe neutropenia (neutrophil < 500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during **Paclitaxel** therapy should have dosage reduced by 20% for subsequent courses of **Paclitaxel.** The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions

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

Preparation for Intravenous Administration

Paclitaxel must be diluted prior to infusion, **Paclitaxel** 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.
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.
Paclitaxel should be administered through an in-line filter with a micro-porous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Stability

Unopened vials of **Paclitaxel** (paclitaxel) injection are stable until the date indicated on the package when stored between 20°-25°C (68°-77°F), 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.

OVERDOSE

There is no known antidote for **Paclitaxel** overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Overdose in pediatric patients may be associated with acute ethanol toxicity.

STORAGE

Store the vials in original cartons between 20°-25°C (68°-77°F). Retain in the original package to protect from light.

HOW SUPPLIED

Paclitaxel 30
Paclitaxel injection USP 30mg/5mL
Multidose vial individually packed in a carton.
Paclitaxel 100
Paclitaxel injection USP 100mg/16.7mL
Multidose vial individually packed in a carton.
Paclitaxel 150
Paclitaxel injection USP 150mg/25 mL
Multidose vial individually packed in a carton.
Paclitaxel 250
Paclitaxel injection USP 250mg/41.7 mL
Multidose vial individually packed in a carton.
Paclitaxel 260
Paclitaxel injection USP 260mg/43.3 mL
Multidose vial individually packed in a carton.
Paclitaxel 300
Paclitaxel injection USP 300mg/50.0 mL
Multidose vial individually packed in a carton.

SHELF LIFE
24 Months

Manufactured in India by:
TAJ PHARMACEUTICALS LTD.
Mumbai, India
at SURVEY NO.188/1 TO 189/1,190/1 TO 4,
ATHIYAWAD, DABHEL, DAMAN- 396210 (INDIA)

This leaflet was last revised in May 2019.

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

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Injection USP Sterile· Multi-Dose Vial
For Intravenous Infusion after dilution
•30mg/ •100mg / •150mg / •250mg/•260mg/ •300mg

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