PACLITAXEL LIPID SUSPENSION FOR INJECTION 30MG/Vial

PaciTol 30 Injection

1. GENERIC NAME

Paclitaxel Lipid Suspension For Injection 30 mg/Vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains :
Paclitaxel IP .....30 mg
Excipients q.s.

3. DOSAGE FORM AND STRENGTH

30 mg vial for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paclitaxel lipid suspension for injection 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 anthracycline unless clinically contraindicated.
- For the adjuvant treatment of node- positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.
- As a first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As a first-line therapy, paclitaxel is indicated in combination with cisplatin.
- 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.
- For the second-line treatment of AIDS-related Kaposi's sarcoma.

4.2 Posology and method of administration

Dosage and procedure of administration can vary based on the cancer types as following.

1. After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel lipid suspension at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.
2. For the adjuvant treatment of node-positive breast cancer, the recommended regimen is paclitaxel lipid suspension, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used 4 courses of doxorubicin and cyclophosphamide.
3. For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks.

a. Paclitaxel lipid suspension 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 lipid suspension administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2

4. For patients with non-small cell lung carcinoma, the recommended regimen, given every 3 weeks, is paclitaxel lipid suspension administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2
5. For patients with AIDS-related Kaposi's sarcoma (KS), paclitaxel lipid suspension 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).

Preparation Guide for Use of Paclitaxel Lipid Suspension

Paclitaxel lipid suspension is supplied as a sterile lyophilized powder for reconstitution before use.

To Avoid errors, READ ENTIRE PREPARATION INSTRUCTION PRIOR TO RECONSTITITION

Aseptic technique must be strictly observed in all handling of paclitaxel lipid suspension. Slowly inject 28ml sterile water for injection, over a period 1-2minute to each paclitaxel lipid suspension vial to yield a preparation containing 1mg/ml of paclitaxel.

Once the injection preparation is complete, allow the vial to sit for a minimum of 5 minute to ensure proper wetting of the lyophilized cake/powder. Gently shake and /or swirl the vial slowly for at least 2 minute until complete dispersion of any cake/powder occurs. Avoid generation of foam, if any.

Paclitaxel lipid suspension forms a light whitish translucent suspension. Visually inspect the vial for particulate matters . Do not use the material if there is any evidence of precipitation or foreign matters. Immediately withdraw (within 10mins) the appropriate dose of Paclitaxel from Paclitaxel lipid suspension vial into sterile syringe using an 18 gauge needle. Inject the syringe contents through the 18- gauge needle, into the appropriate amount of 5% Dextrose injection so as to achieve a final concentration of approximately between 0.3mg/ml to 0.5mg/ml prior to the administration.

Mix the infusion thoroughly by manual rotation. As with all parenteral products, Paclitaxel lipid suspension should be inspected visually for particulate matter or discoloration prior to administration.

THE USE OF AN IN LINE FILTER IS NOT RECOMMENDED DURING INFUSION

Any unused material must be discarded .

Use within 8 Hours of reconstitution/ Dilution

4.3 Contraindications

Paclitaxel lipid suspension is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel.

Paclitaxel lipid suspension should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1,000 cells/mm^3.

4.4 Warnings and Precautions

Patients who have severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug. 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.

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 1,500 cells/mm^3 (<1,000 cells/mm^3 for patients with KS). Frequent monitoring of blood counts should be conducted during paclitaxel treatment. Patients should not be retreated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 (>1,000 cells/mm^3 for patients with KS) and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been reported in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. 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.

Hematology

Paclitaxel lipid suspension 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 lipid suspension.

As reported earlier, patients should not be retreated with subsequent cycles of paclitaxel lipid suspension until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of therapy, a 20% reduction in dose for subsequent courses of paclitaxel lipid suspension therapy is recommended.

In patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, the recommended dose of paclitaxel lipid suspension for this disease, can be initiated and repeated if the neutrophil count is at least 1,000 cells/mm^3.

Hypersensitivity Reactions

No routine premedication (e.g. corticosteroids) prior to paclitaxel lipid suspension administration is necessary for prevention of Infusion related reaction (IRRs). However, patients with a history of severe hypersensitivity reactions to paclitaxel should not be treated with paclitaxel lipid suspension. Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity 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. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. Use of paclitaxel lipid suspension in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Nervous System

Peripheral neuropathy is frequent with paclitaxel; the development of severe symptomatology unusual and requires a dose reduction of 20% for all subsequent courses of treatment cycle. In the clinical trial of paclitaxel lipid suspension, peripheral neuropathy was reported in 3 (6.66%) patients who received paclitaxel lipid suspension at 80mg/ m^2. However, none of the patients receiving 175 mg/m^2 of paclitaxel lipid suspension or conventional paclitaxel every 3 weeks experienced any peripheral neuropathy.

Hepatic

There is limited evidence that the myelotoxicity of paclitaxel may be exacerbated in patients with serum total bilirubin >2 times ULN. Extreme caution should be exercised when administering paclitaxel to such patients

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation may occur in patients being treated with paclitaxel lipid suspension. A specific treatment for extravasation reactions 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 lipid suspension has not been studied.

It has been reported that paclitaxel is clastogenic in vitro (chromosome aberrations in human lymphocytes) and in vivo (micronucleus test in mice). Paclitaxel was not mutagenic in the Ame 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, 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.

4.5 Drug Interactions

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

Caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CTP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (e.g., midazolam buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g. atazanavir, clarithromycin, indinavir, etaconazole, ketoconazole, nefazodone, nelfinavir, ritonavir saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g.rifampin) of CYP2C8.

Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

4.6 Use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.)

Pregnancy

Paclitaxel can cause fetal harm when administered to a pregnant woman. Paclitaxel lipid suspension has not been tested in pregnant patients. It has been reported that administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on mg/m^2 basis) caused embryo- and fetotoxicity, as toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal (about 1/15 the daily maximum recommended human dose on mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel 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 child bearing potential should be advised to avoid becoming pregnant.

Nursing mothers

It is not known whether the drug is excreted in human milk. It has been reported that following intravenous administration of carbon 14 labeled paclitaxel 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

No specific study with paclitaxel lipid suspension in geriatric population was conducted. In most studies reported, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied.

4.7 Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability.

4.8 Undesirable effects

The most serious adverse reactions from paclitaxel lipid suspension were alopecia, neutropenia, back pain, anemia and urinary tract infections.

Hematologic

Neutropenia, the most important hematologic toxicity of paclitaxel, is dose and schedule dependent and is generally rapidly reversible.

In the clinical trial, the incidence of neutropenia with paclitaxel lipid suspension 175 mg/m^2 Q3W, 80 mg/m^2 QW and paclitaxel 175 mg/m^2 Q3W arms was 31.25%, 44.44% and 7.41% respectively.

The incidence of anemia with paclitaxel lipid suspension 175 mg/m^2 Q3W, 80 mg/m^2 QW and paclitaxel 175 mg/m^2 Q3W arms was 16.67%, 44.44% and 18.52% respectively.

The incidence of thrombocytopenia in paclitaxel lipid suspension 175 mg/m^2 Q3W and 80 mg/m^2 QW arms was 10.42%, and 2.22% respectively.

Hypersensitivity Reactions (HSRs):

No routine premedication prior to paclitaxel lipid suspension administration is necessary for prevention of Infusion related reaction (IRRs). Clinical signs and symptoms indicative of an IRR may include flushing, tachycardia, hypertension or hypotension, rash or hives, fever with chills, rigors, hypoxia or dyspnea, as well as back, flank, chest, or abdominal pain. These reactions may be transient. When such signs and symptoms are observed, the infusion should be interrupted and supportive care administrated immediately according to the institution's protocol for treating such events.

None of the patients receiving 175 mg/m^2 of paclitaxel lipid suspension every 3 weeks experienced any hypersensitivity reactions.

Cardiovascular:

Treatment with paclitaxel lipid suspension may result in significant cardiovascular events possibly related to single-agent paclitaxel may occur in approximately 1% of all patients as was observed by paclitaxel injection. These events may include syncope, rhythm abnormalities, hypertension, and venous thrombosis. It has been reported that in patients treated with paclitaxel, the electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities did not usually result in symptoms, were not dose-limiting, and required no intervention.

Cases of myocardial infarction have been reported with paclitaxel. Congestive heart failure, including cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure, has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Atrial fibrillation and supraventricular tachycardia have been reported.

Respiratory

Interstitial pneumonia, lung fibrosis, and pulmonary embolism have been reported with paclitaxel.

Radiation pneumonitis may occur in patients receiving concurrent radiotherapy.

Pleural effusion and respiratory distress have been reported.

In the clinical trial, the incidence of cough in paclitaxel lipid suspension 175 mg/m^2 Q3W, 80 mg/m^2 QW and conventional paclitaxel 175 mg/m^2 Q3W arms was 4.17%, 22.22% and 7.41% respectively.

Neurologic

In clinical trial of paclitaxel lipid suspension, peripheral neuropathy was reported in 3 patients who were receiving paclitaxel lipid suspension at 80 mg/m^2.

However, none of the patients receiving 175 mg/m^2 of paclitaxel lipid suspension every 3 weeks experienced any peripheral neuropathy.

These patients were also not pre-medicated with corticosteroids.

Hepatic

No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Renal

Patients with gynecological cancers treated with paclitaxel and cisplatin may increase the risk of renal failure with the combination therapy of paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

Gastrointestinal (GI)

Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, dehydration, esophagitis, constipation, and ascites have been reported with paclitaxel. Neutropenic enterocolitis (typhlitis), despite the co-administration of filgraslim, was observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

In the clinical trial, the incidence of diarrhea in paclitaxel lipid suspension 175 mg/m^2 Q3W and 80 mg/m^2 QW and conventional paclitaxel 175 mg/m^2 Q3W arms was 2.08%, 8.88% and 3.7% respectively. The incidence of nausea in paclitaxel lipid suspension 175 mg/m^2 Q3W, 80 mg/m^2 QW and conventional paclitaxel 175 mg/m^2 Q3W arms was 4.16%, 6.66% and 3.7% respectively.

The incidence of vomiting in paclitaxel lipid suspension 175mg/ m^2 Q3W and 80 mg/m^2 QW arms was 6.25%, and 11.11% respectively.

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, reported with paclitaxel are usually mild and consist 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.

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported with paclitaxel. 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.

4.9 Overdose

There is no known antidote for paclitaxel overdosage. Theprimary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential forvital 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.

5.2 Pharmacodynamic Property

Pharmacotherapeutic group: antineoplastic agents (taxanes).

Clinical Studies

Locally Advanced or Metastatic Breast Cancer

An open label, randomized, multiple dose, parallel study was conducted in locally advanced or metastatic breast cancer patients after failure of prior chemotherapy.

Females, ≥ 18 years and ≤ 65 years of age, with histopathologically/ cytologically confirmed breast cancer, having locally advanced or metastatic breast cancer after failure of prior chemotherapy, having Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, having adequate bone marrow, renal and hepatic function, having at least one measurable lesion as per the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1), having life expectancy of at least 6 months were randomized to receive either paclitaxel lipid suspension or Taxol. A total of 120 patie nts with locally advanced or metastatic breast cancer, after failure of prior chemotherapy, were randomized in the ratio 2:2:1 (NPLS every three weeks:NPLS weekly: Taxol every three weeks) and enrolled into the study. Patients were administered paclitaxel lipid suspension (n= 48) or Taxol (n= 27) at 175 mg/m^2 as per randomization schedule, by IV infusion for 3 hours in each cycle of 21 days in Arm A and Arm C respectively. Each patient received maximum of 6 cycles of paclitaxel lipid suspension or Taxol.

In Arm B, patients were administered weekly with paclitaxel lipid suspension att he dose of 80 mg/m^2 (n= 45) for 18 weeks. Patients in the paclitaxel lipid suspension groups (Arm A and Arm B) were not premedicated whereas patients treated with Taxol were premedicated as per the prescribing information.

Each drug, paclitaxel lipid suspension (Arm A. 175 mg/m^2 / Arm B, 80 mg/m^2) or Taxol (Arm C, 175 mg/m^2) was administered by IV infusion over 3 hours. Disease status and tumor response (CT Scan/MRI) was assessed after every 2 cycles of treatment using RECIST 1.1 guidelines through cycle 6 (including confirmation of response if required). Independent evaluation (blinded reading) of the images acquired in clinical trial was done by Central Imaging Facility.

The primary efficacy evaluation was based on the overall response rate (CR + PR), defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR) after receiving study treatment with paclitaxel lipid suspension or Taxol. The secondary efficacy endpoint was based on the disease control rate (DCR = CR + PR + SD), defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR) or stable disease (SD).

A point estimate and a two-sided 95% confidence interval (CI) were computed for the secondary efficacy endpoint, disease control rate (CR+PR+SD) from best overall response of the two treatment groups and their difference.

The overall response rate (CR+ PR) was 36.4% (95% CI, 22.1- 50.6%) for paclitaxel lipid suspension treatment- [Arm A (175 mg/m^2)] administered every 3 weeks, 46.5% (95% CI, 31.6- 61.4%) for paclitaxel lipid suspension treatment- [Arm B (80 mg/m^2)] administered every week and 20.8% (95% CI, 4.6- 37.1%) for Taxol treatment- [Arm C (175 mg/m^2)] administered every 3 weeks. The disease control rates were 86.4%, 88.4% and 83.3% for Arm A, Arm B and Arm C respectively.

A total of 450 adverse events (AEs) reported in 97 patients during the course of the trial. 157 AEs occurred to patients under paclitaxel lipid suspension Arm A (n=48), 239 AEs occurred to patients under paclitaxel lipid suspension Arm B (n=45) and 54 AEs occurred to patients under Taxol Arm C (n=27). The paclitaxel lipid suspension treated patients were not given any premedication including corticosteroids. The AEs related t o paclitaxel lipid suspension Arm A, paclitaxel lipid suspension Arm B and Taxol Arm C were 68.75%, 68.89% and 48.15% respectively. In both paclitaxel lipid suspension and Taxol treatment groups one or more Grade 3 or 4 treatment-related adverse events were observed. The percentage of patients reporting serious Grade 4 AEs in Arm A, Arm Band Arm C were 6.25%, 11.11% and 7.41% respectively.

Overall, the investigational drugs were found to be well tolerated. Majority of the post-dose AEs resolved without any sequelae despite the fact patients were not pre-medicated with corticosteroids or anti-allergic treatment in paclitaxel lipid suspension treatment groups.

5.3 Pharmacokinetic Property

An open label, balanced, randomized, 2- period, 2-treatment, 2-sequence, and 2-way crossover study was conducted to evaluate safety and pharmacokinetic comparison of intravenous infusion of paclitaxel lipid suspension and Taxol in patients with metastatic breast cancer.

16 patients were dosed at 175 mg/m^2 intravenously, over 3 hours once every three weeks. In Period I, patients were dosed with test or reference product on the first day of the chemotherapy cycle (day 1) of the study as per the randomization schedule. In Period II, patients were crossed over to either test or reference product (patients on test product to be crossed over to reference product and vice-versa) on the first day of the next chemotherapy cycle (day 22) as per randomization schedule. The pharmacokinetics evaluations were done by collecting whole blood samples from patients (both test and reference product) prior to each dose and over a period of 51-hour after each dose. The log transformed Test/Reference ratios for Cmax and AUC_{0-t} were about 29.5% and 44.8% respectively. The safety profile of paclitaxel lipid suspension was similar to that of Taxol.

6. Nonclinical properties

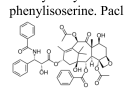
6.1 Animal Toxicology or Pharmacology

Non Clinical Toxicological Studies

A sub chronic 28 days intravenous toxicity study was conducted by five consecutive days administration of paclitaxel lipid suspension in Swiss Albino mice at 5 mg/kg, 10 mg/kg or 15 mg/kg. The results showed in no hematological abnormalities related to the treatment in all groups. Biochemical analysis revealed no abnormalities at 5 and 10 mg/kg dose but elevated levels of Alanine Aminotransferase and Alkaline Phosphatase was observed at the highest dose (15 mg/kg). Gross and histopathological changes were observed in male and female animals at 10 and 15 mg/kg. Mortalities (1/6 males and 1/6 females) were noted in animals treated with highest dose (15 mg/kg) of the paclitaxel lipid suspension. The results were consistent with Taxol where the maximum tolerated dose of Taxol in mice was determined to be over 12.5 mg/kg.

7. Description

Paclitaxel is a natural product with antitumor activity. It is obtained via a semi-synthetic process from Taxus baccata. The chemical name for 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 hast 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.

The paclitaxel lipid suspension formulation is a sterile lyophilized powder containing Soy phosphalidylcholine and Sodium Cholesteryl Sulphate with 30 mg paclitaxel per vial. Each 30 mg vial is first reconstituted by adding 28 ml of sterile water to yield 1 mg/ml of paclitaxel lipid suspension. The reconstituted suspension can further be diluted with 5% dextrose Injection IP prior to administration.

8. Pharmaceutical particulars

8.1 Incompatibilities: Not applicable

8.2 Shelf-life: Two years

8.3 Packaging information: Each single dose vial is packed in a carton

8.4 Storage and handing instructions: Store at 2°-8°C. Do not freeze. Protect from light. Keep out of reach of children.

9. Patient Counselling Information

Advise the patient to read the approved patient labeling (Patient Information).

Hematologic Effects: Patients must be informed of the risk of low blood cell counts and severe and life-threatening infections and instructed to contact their healthcare provider immediately for fever or evidence of infection. [see Warnings and Precautions]

Nervous System: Patients must be informed that sensory neuropathy occurs frequently with Paclitaxel and patients should advise their healthcare providers of numbness, tingling, pain or weakness involving the extremities. [see Warnings and Precautions]

Pneumonitis: Instruct patients to contact their healthcare provider immediately for sudden onset of dry persistent cough, or shortness of breath. [see Warnings and Precautions]

Hypersensitivity: Instruct patients to contact their healthcare provider for signs of an allergic reaction, which could be severe and sometimes fatal. [see Warnings and Precautions]

Common Adverse Reactions: Explain to patients that alopecia, fatigue/asthenia, and myalgia/ar- hralgia occur frequently with paclitaxel.

Patients should be instructed to contact their healthcare providers for persistent vomiting, diarrhea, or signs of dehydration.

Embryo-Fetal Toxicity: Paclitaxel injection can cause fetal harm. Advice patients to avoid becoming pregnant while receiving this drug.

Females of reproductive potential should use effective contraception during treatment with Paclitaxel and for at least six months after the last dose of paclitaxel.

Advise male patients with female partners of reproductive potential to use effective contraception and avoid fathering a child during treatment withpaclit axel and for at least three months after the last dose of paclitaxel.

Advise patients not to breast feed while taking paclitaxel and for two weeks after receiving the last dose.

Storage Condition :

Store at 2-8°C. Do not freeze. Protect from light.

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