141.0 mm

206.0 mm

Petaxel Injection
(Paclitaxel)

پیٹاکسِل انجیکشن
(پیکلیٹیکسل)
۱۵۰ ملی گرام/۲۵ ملی لیٹر
۳۰۰ ملی گرام/۵۰ ملی لیٹر

COMPOSITION:
Petaxel Injection 150mg/25ml
Each 25ml vial contains:
Paclitaxel.....150mg
(USP Specifications)
Petaxel Injection 300mg/50ml
Each 50ml vial contains:
Paclitaxel.....300mg
(USP Specifications)

DESCRIPTION

PETAXEL (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. PETAXEL (paclitaxel) 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.

PHARMACOLOGY

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 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 **PETAXEL**, 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. It appeared that with the 24-hour infusion of PETAXEL, a 30% increase in dose (135 mg/m2 vs 175 mg/m2) increased the Cmax by 87%, whereas the AUC (0-∞) 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 PETAXEL, ranged from 227 to 688 L/m2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m2 given by 1-hour infusions (n=15), 30 to 275 mg/m2 given by 6- hour infusions (n=36), and 200 to 275 mg/m2 given by 24-hour infusions (n=54) in Phase 1 and 2 studies. Values for CLT and volume of distribution were consistent with the findings in the Phase 3 study. The pharmacokinetics of PETAXEL in patients with AIDS-related Kaposi's sarcoma have notbeen studied.

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 µg/mL, indicate that between 89 to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m2 doses of PETAXEL as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m2 dose of radiolabeled PETAXEL as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α- hydroxypaclitaxel, accounted for the balance. In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-pdihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6αhydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

INDICATIONS AND USAGE

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

PETAXEL is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor negative tumors.

PETAXEL 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.

PETAXEL, 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.

PETAXEL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized 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 PETAXEL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to PETAXEL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before PETAXEL, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to PETAXEL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before PETAXEL.

Ovarian Cancer:

For patients with carcinoma of the ovary, the following regimens are recommended:

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.
2) **PETAXEL** administered intravenously over 3 hours at a dose of 175 mg/m2 followed by cisplatin at a dose of 75 mg/mg; or b.
3) **PETAXEL** administered intravenously over 24 hours at a dose of 135 mg/m2 followed by cisplatin at a dose of 75 mg/m2. 2) In patients previously treated with chemotherapy for carcinoma of the ovary, PETAXEL has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is PETAXEL 135 mg/m2 or 175 mg/m2 administered intravenously over 3 hours every 3 weeks.

Breast Cancer:

For patients with carcinoma of the breast, the following regimens are recommended:

1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is PETAXEL, at a dose of 175 mg/m2 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.
2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, PETAXEL at a dose of 175 mg/m2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

Non-Small Cell Lung Cancer: For patients with non-small cell lung carcinoma, the recommended regimen, given every 3 weeks, is PETAXEL administered intravenously over 24 hours at a dose of 135 mg/m2 followed by cisplatin, 75 mg/m2.

AIDS Related Kaposi`s Sarcoma:

For patients with AIDS-related Kaposi's sarcoma, PETAXEL administered at a dose of 135 mg/m2given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45– 50 mg/m2/week). In the 2 clinical trials evaluating these schedules, the former schedule (135 mg/m2 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/m2 every 2 weeks). Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

1) Reduce the dose of dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead of 20mg PO);
2) Initiate or repeat treatment with PETAXEL only if the neutrophil count is at least 1000 cells/mm3;
3) Reduce the dose of subsequent courses of PETAXEL by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm3 for a week or longer); and
4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of PETAXEL should not be repeated until the neutrophil count is at least 1500 cells/mm3 and the platelet count is at least 100,000 cells/mm3. PETAXEL should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm3. Patients who experience severe neutropenia (neutrophil <500 cells/mm3 for a week or longer) or severe peripheral neuropathy during PETAXEL therapy should have dosage reduced by 20% for subsequent courses of PETAXEL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

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.

PREPARATION FOR INTRAVENOUS ADMINISTRATION

PETAXEL (paclitaxel) Injection must be diluted prior to infusion. PETAXEL 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 1.2mg/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.

Data collected for the presence of the extractable plasticizer DEHP [di-(2ethylhexyl) phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. **PETAXEL** solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

PETAXEL should be administered through an in-line filter with a microporous 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.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of **PETAXEL** since they can cause the stopper to collapse resulting in loss of sterile integrity of the PETAXEL solution.

OVERDOSAGE

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

WARNINGS

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 PETAXEL 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 **PETAXEL** should not be rechallenged with the drug.

Severe conduction abnormalities have been documented in <1% of patients during PETAXEL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during PETAXEL infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PETAXEL.

PREGNANCY

PETAXEL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m2 basis); teratogenic potential could not be assessed at higher doses due to extensive.

DRUG INTERACTIONS:

In a Phase 1 trial using escalating doses of PETAXEL (110– 200 mg/m2) and cisplatin (50 or 75 mg/m2) given as sequential infusions, myelosuppression was more profound when PETAXEL was given after cisplatin than with the alternate sequence (ie, PETAXEL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when PETAXEL was administered following cisplatin.

The metabolism of PETAXEL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when PETAXEL is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when PETAXEL is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Potential interactions between PETAXEL, 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. Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Cardiovascular:

Hypotension, bradycardia, and hypertension have been observed during administration of PETAXEL, but generally do not require treatment. Occasionally PETAXEL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of PETAXEL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

Nursing Mothers:

It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon 14-labeled PETAXEL 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 PETAXEL therapy.

Pediatric Use:

The safety and effectiveness of PETAXEL (paclitaxel) in pediatric patients have not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which PETAXEL was infused intravenously over 3 hours at doses ranging from 350 mg/m2 to 420 mg/m2. The toxicity is most likely attributable to the high dose of the ethanol component of the PETAXEL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of PETAXEL for use in this population.

Geriatric Use:

Of 2228 patients who received PETAXEL in 8 clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive PETAXEL 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 2 clinical studies in NSCLC, the elderly patients treated with PETAXEL had a higher incidence of cardiovascular events. 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.

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. Recurrence of skin reactions at a site of previous extravasation following administration of PETAXEL at a different site, ie, "recall," has been reported.

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

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.

Other Clinical Events:

Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to PETAXEL- related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with PETAXEL administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study

Storage & Instructions:

Unopened vials of PETAXEL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Protect from sunlight, heat and moisture. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the PETAXEL 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.

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED

Petaxel Injection 150mg/25 ml:
1 vial

Petaxel Injection 300mg/50 ml:
1 vial

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۲۰- ۲۵ ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔

دھوپ اور گرمی سے محفوظ رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.