

Manufactured By
Beacon Pharmaceuticals PLC
Bhaluka, Mymensingh, Bangladesh

LF-47602

CYTOTOXIC DRUG

FOR IV USE ONLY

COMPOSITION

Xelpac Premium 30 Injection: Each vial contains 5 mL solution containing Paclitaxel USP 30 mg (6 mg/mL).

Xelpac Premium 100 Injection: Each vial contains 16.7 mL solution containing Paclitaxel USP 100 mg (6mg/mL).

Xelpac Premium 260 Injection: Each vial contains 43.4 mL solution containing Paclitaxel USP 260 mg (6mg/mL).

Xelpac Premium 300 Injection: Each vial contains 50 mL solution containing Paclitaxel USP 300 mg (6 mg/mL).

CLINICAL INFORMATION

Therapeutic Indications

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

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

• It is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

• It is 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.

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

PHARMACOLOGICAL INFORMATION

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.

MECHANISM OF ACTION

Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

PHARMACOKINETICS

Following intravenous administration of 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. Pharmacokinetic parameters of Paclitaxel following 3 and 24 hour infusions at dose levels of 135 and 175 mg/m² were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

TABLE 1: Summary of pharmacokinetic parameters - mean values

DOSE (mg/m ²)	Infusion Duration(H)	N (patients)	Cmax (ng/mL)	AUC (0-a) (ng•h/mL)	T-Half (h)	CLT (L/h/m ²)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

Cmax = Maximum plasma concentration

AUC (0-a) = Area under the plasma concentration - time curve from time 0 to infinity

CL_T = Total body clearance

DOSE & 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 Paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Nonpolyvinyl (non-PVC) administration sets (which are

polyethylene-lined) should be used.

Paclitaxel should be administered through I.V. tubing containing an in-line filter with a microporous membrane NOT >0.22µm. Use of filter devices such as IVEX-2 filters (which incorporate short inlet and outlet polyvinyl chloride-coated tubing) has not resulted in significant leaching of DEHP.

PREMEDICATION

All patients should be premedicated prior to Paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of:

- Dexamethasone 20 mg PO or 8 mg I.V. administered approximately 12 and 6 hours prior.

- Diphenhydramine 50 mg (or its equivalent-Promethazine HCl 25 mg) I.V. 30 -

60 minutes prior.

- Cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 - 60 minutes prior.

SPECIAL INSTRUCTION FOR USES, HANDLING AND DISPOSAL

Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Xelpac. The use of gloves is recommended. If Paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposures, 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 extravasations, it is advisable to closely monitor the infusion site for possible infiltration during drug

administration. All broken containers must be treated with the same precautions and regarded as contaminated waste. Contaminated waste is to be disposed of by incineration in rigid containers labeled for this purpose or must be destroyed as per the government rule.

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, 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. 500 ml Xenosol (Normal Saline) to be used for dilution. 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-(2-ethylhexyl) 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. Paclitaxel 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. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

INTRAVENOUS INFUSION AND DOSAGE

Ovarian Cancer

First line treatment in combination with cisplatin

- Paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m² followed by cisplatin at a dose of 75 mg/m² every 3 weeks

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

Breast Cancer

- 175 mg/m² administered I.V. over 3 hours every 3 weeks has been shown to be effective after failure of chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

AIDS-related Kaposi's sarcoma

- 135 mg/m² given I.V. over 3 hours every 3 weeks or at a dose of 100 mg/m² given I.V. over 1 hour every 3 weeks every 3 weeks is recommended (dose intensity 45-50 mg/m²/week).

Lung Cancer

- For the first-line treatment of NSCLC, in combination with cisplatin, in patients

who are not candidates for potentially curative surgery and/or radiation therapy. - 135 mg/m² I.V. administered over 24 hours followed by Cisplatin. The regimen to be repeated every 3 weeks based on the clinical status of the patient. Yr¹

Gastric Cancer

- Once daily 210 mg/m² (Body surface area) by 3 hour intravenous infusion for adults. At least 3 week of dosing interval is of absolute necessity.

Dosage modification for toxicity (solid tumors, including ovary, breast, and lung carcinoma)

Courses of Paclitaxel should not be repeated until the neutrophil count is ≥ 1500 cells/mm³ and the platelet count is ≥ 100,000 cells/mm³; reduce dosage

by 20% for patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm³ for a week or longer).

Dosage modification for immuno suppression in advanced HIV disease

Paclitaxel should not be given to patients with HIV if the baseline or subsequent neutrophil count is <1000 cells/mm³. Additional modifications include: Reduce dosage of dexamethasone in premedication to 10 mg orally; reduce dosage by 20% in patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm³ for a week or longer); initiate concurrent hematopoietic growth factor (G-CSF) as clinically indicated.

Dosage adjustment in hepatic impairment

These recommendations are based upon the patient's first course of therapy where the usual dose would be 135 mg/m² dose over 24 hours or the 175 mg/m² dose over 3 hours in patients with normal hepatic function. Dosage in subsequent courses should be based upon individual tolerance. Adjustments for other regimens are not available.

24-hour Infusion

If transaminase levels <2 times upper limit of normal (ULN) and bilirubin level 1.5 mg/dL : 135 mg/m²

If transaminase levels 2-<10 times ULN and bilirubin level 1.5 mg/dL : 100 mg/m²

If transaminase levels <10 times ULN and bilirubin level 1.6-7.5 mg/dL : 50 mg/m²

If transaminase levels 10 times ULN and bilirubin level >7.5 mg/dL : Avoid use

3-hour Infusion

If transaminase levels <10 times ULN and bilirubin level 1.25 times ULN : 175 mg/m²

If transaminase levels <10 times ULN and bilirubin level 1.26-2 times ULN : 135 mg/m²

If transaminase levels <10 times ULN and bilirubin level 2.01-5 times ULN : 90 mg/m²

If transaminase levels 10 times ULN and bilirubin level >5 times ULN : Avoid use

STABILITY

Unopened vials of Paclitaxel 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.

complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

CONTRAINDICATIONS

- Patients with a known hypersensitivity to Paclitaxel or other drugs formulated in Cremophor EL (polyoxethylated castor oil).

- Paclitaxel should not be used in patients with solid tumors who have baseline neutrophil counts of < 1500 cells/mm³ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of < 1000 cells/mm³.

WARNING

Paclitaxel Injection should be administered under the supervision of a

physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2-4% of patients receiving Paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premeditation. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to Paclitaxel should not be rechallenged with the drug.

Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm³ and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil

count is less than 1,000 cells/mm³. 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.

SIDE EFFECTS

Data given below is based on the pooled analysis of 812 patients with solid tumors enrolled in 10 studies. The frequency and severity of adverse events have been generally similar for patients receiving Paclitaxel for the treatment with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, febrile neutropenia and GI toxicities. These patients require a lower dose intensity and supportive care.

Hypersensitivity Reactions (HSR)

The frequency and severity of HSRs is not affected by the dose or schedule of Paclitaxel administration. These are conserved in 20% of all courses and in 41% of all patients. The most frequent symptoms observed are dyspnea, Flushing, chest pain and tachycardia. Rare reports of chills and reports of back pain associated with HSRs have been received.

Cardiovascular

Hypotension, during the first 3 hours of inclusion, occurs in 12% of all patients and 3% of all courses administered. The frequency of hypotension and bradycardia are not influenced by prior antihypertensive therapy, nor by the dose or the schedule. Significant cardiovascular events possibly related to Paclitaxel occur in approximately 1% of all patients. These events include syncope,

rhythm abnormalities, hypertension and venous thrombosis. The arrhythmias include asymptomatic ventricular tachycardia bigeminy and complete AV block requiring pacemaker placements. ECG abnormalities are noted in 23% of the patients. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Central Nervous System

The frequency and severity of neurologic manifestations are dose -dependent, but are not influenced by infusion duration. Peripheral neuropathy is observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency increases with cumulative dose. Neurologic symptoms are observed in 27% patients after the first course of treatment and in 34-51% from course 2 to 109. sensory symptoms usually

improve or resolve within several months of Paclitaxel discontinuation. The incidence of neurologic symptoms does not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for Paclitaxel therapy. Other serious neurologic events have been rare (<1%) and include grand mal seizures, syncope, ataxia and neuroencephalopathy. Rare reports of reversible autonomic neuropathy resulting in paralytic ileus have also been observed.

Gastrointestinal

Mild to moderate nausea/vomiting, diarrhea and mucositis are reported by 52%, 38% and 31% of all patients, respectively. Mucositis is schedule dependent and occurs more frequently with the 24-hour than with 3-hour infusion. Rare reports of intestinal obstruction, intestinal perforation,

pancreatitis, ischemic colitis and dehydration have been received.

Kidney/Genitourinary

Urinary tract infections are frequently reported infectious complications. Among the patients treated for Kaposi's sarcoma with Paclitaxel, renal toxicity of grade III and IV severity has been reported.

Liver

No relationship is observed between liver function abnormalities and either dose or schedule of Paclitaxel administration. Among patients with normal baseline liver function 7%, 22%, and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to Paclitaxel

is not associated with cumulative hepatic encephalopathy leading to death have been documented.

Respiratory

Upper respiratory tract infections do occur. Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Musculo-skeletal

There is no consistent relationship between dose or schedule of Paclitaxel and the frequency or severity of arthralgia/myalgia. 60% of all patients treated

experience arthralgia/myalgia, 8% experience severe symptoms. The symptoms are usually transient, occur 2-3 day after Paclitaxel administration and resolve within a few days. The frequency and severity of musculoskeletal symptoms remain unchanged throughout the treatment period.

Injection Site Reactions

These include reactions secondary to extravasations, are usually mild and consist of erythema, tenderness, skin discoloration, or swelling at the injection site. These are observed more frequently with the 24-hour infusion than with the 3-hour infusion. Rare reports of more severe events such as phlebitis, cellulitis, indurations, skin exfoliation, necrosis and fibrosis have been documented. It is advisable to closely monitor the infusion site for possible infiltration during drug administration.

OTHER CLINICAL EVENTS

Alopecia is observed in almost all (87%) of the patients. Nail changes are uncommon (2%). Edema has been reported in 21% of all patients. Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash and pruritus have been documented.

Pregnancy

If Paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the bearing should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers

It is not known whether the drug is excreted in human milk.

Pediatric Use

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

Patients with hepatic impairment

Hepatic impairment has a great influence on the systemic exposure of Paclitaxel and metabolites with pharmacodynamic consequences. A decrease of biliary elimination is probably the major mechanistic effect that influences Paclitaxel metabolism and elimination. Specific dosing guidelines are not

available. In general, dosage reductions of at least 50% are recommended in patients with moderate or severe hyperbilirubinemia or substantially increased serum transferase levels.

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 of 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/m² basis). At this dose, Paclitaxel caused reduced fertility and reproductive indices, and

increased embryo- and fetotoxicity.

Drug Interactions

Substrate (major) of CYP2C8/9, 3A4; Induces CYP3A4.

Carboplatin, Cisplatin (platinum derivatives): When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives to limit myelosuppression and to enhance efficacy.

CYP2C8/9 Inducers: May decrease the levels/effects of paclitaxel. Example inducers include carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, and secobarbital.

CYP2C8/9 Inhibitors: May increase the levels/effects of paclitaxel. Example inhibitors include delavirdine, fluconazole, gemfibrozil, ketoconazole, nifedipine, NSAIDs, pioglitazone, and sulfonamides.

CYP3A4 Inducers: CYP3A4 inducers may decrease the levels/effects of Paclitaxel. Example inducers include amloglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifampin.

CYP3A4 Inhibitors: May increase the levels/effects of paclitaxel. Example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nifedipine, propofol, protease inhibitors, quinidine, and verapamil.

Doxorubicin:

-Paclitaxel may increase doxorubicin levels/toxicity.

-Monitoring Parameters.

-Monitor for hypersensitivity reactions.

PRESENTATION AND PACKAGING

Xelpac Premium 30 Injection : Each box contains one multi-dose vial of 5 mL solution.

Xelpac Premium 100 Injection : Each box contains one multi-dose vial of 16.7 mL solution.

Xelpac Premium 260 Injection : Each box contains one multi-dose vial of 43.4 mL and 1 piece of 20 mL disposable syringe with 21-gauge needle.

Xelpac Premium 300 Injection: Each box contains one multi-dose vial of 50 mL solution, 500 mL Normal Saline, DEHP Free Infusion Set with precision filter and 1 piece of 20 mL disposable syringe with 21-gauge needle.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store the vial in original carton below 30°C, away from light. Keep out of the reach of children.

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