135x142mm (front-back)

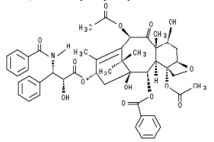
PACLITAXEL INJECTION IP
30mg/5ml, 100mg/16.7ml, 260mg/43.4ml

WEMPACLI® 30/100/260
Injection

COMPOSITION
Each ml contains:

Paclitaxel	IP	6 mg
Polyoxyl 35 Castor Oil	IP	527 mg
Dehydrated Alcohol	IP	49.7% v/v

DESCRIPTION
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 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 has the following structural formula:



CLINICAL PHARMACOLOGY
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. Following intravenous administration, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug.

INDICATIONS AND USAGE
Ovarian cancer:
In first line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced disease or a residual disease (> 1cm) after initial laparotomy, in combination with cisplatin.
In second-line chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum based therapy.
Breast cancer:
In the adjuvant setting, paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.
Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.
As a single agent, treatment of metastatic carcinoma of the breast in patients who have failed to respond adequately to standard treatment with anthracyclines or in whom anthracycline therapy has not been appropriate.
Advanced non-small cell lung cancer (NSCLC):
Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgical intervention and/or radiation therapy.
AIDS-related Kaposi's sarcoma (KS):
Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy.

DOSAGE & ADMINISTRATION
Dosage
Pre-medication: All patients must be given pre-medication consisting of corticosteroids, antihistamines and H_2-receptor antagonists prior to paclitaxel administration, in order to prevent severe hypersensitivity reactions. Such pre-medication may consist of:

Table 1: Pre-medication Schedule

Pre-medication	Dose	Administration Prior to Paclitaxel
Dexamethasone	20 mg oral* or IV**	Oral: Approx. 12 and 6 hours IV: 30 – 60 min
Diphenhydramine ***	50 mg IV	30 to 60 min
Cimetidine or Ranitidine	300 mg IV 50 mg IV	30 to 60 min

* 8-20 mg for KS patients
** intravenous
*** or an equivalent antihistamine e.g. chlorphenamine 10 mg IV, administered 30 to 60 minutes prior to paclitaxel

Paclitaxel should be administered using an in-line filter with a microporous membrane of ≤0.22 microns.
Given the possibility of extravasation, it is advisable to monitor closely the infusion site for possible infiltration during administration
First-line treatment of ovarian cancer: Although alternative medication regimens for paclitaxel are under investigation at present, a combination therapy of paclitaxel and cisplatin is recommended.
Depending on the duration of infusion, two different dosages are recommended for paclitaxel treatment: 175 mg/m^2 of paclitaxel is administered as an intravenous infusion over a period of three hours followed thereafter by 75 mg/m^2 of cisplatin and the therapy is repeated at 3-week intervals, or 135 mg/m^2 of paclitaxel is administered as an intravenous infusion over a period of 24 hours followed thereafter by 75 mg/m^2 of cisplatin and the therapy is repeated at 3-week intervals.
Second-line treatment of ovarian cancer: The recommended dose of paclitaxel is 175 mg/m^2 administered over 3 hours, with a 3-week interval between courses.
Adjuvant chemotherapy in breast carcinoma: The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.
First-line chemotherapy of breast carcinoma: When used in combination with doxorubicin (50 mg/m^2), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses.
When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.
Second-line chemotherapy of breast carcinoma: The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours, with a 3-week interval between courses.
Advanced non-small cell lung cancer: The recommended dose of paclitaxel is 175 mg/m^2 administered over 3 hours followed by 80 mg/m^2 of cisplatin, with a 3-week interval between courses.
Treatment of AIDS-related KS: The recommended dose of paclitaxel is 100 mg/m^2 administered as a 3-hour intravenous infusion every two weeks.
Dose adjustment: Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be re-administered until the neutrophil count is ≥1.5 x 10^9/l (≥1 x 10^9/l for KS patients) and the platelet count is ≥100 x 10^9/l (≥75 x 10^9/l for KS patients).
Patients who experience severe neutropenia (neutrophil count <0.5 x 10^9/l for a minimum of 7 days) or severe peripheral neuropathy, should receive a dose reduction of 20% for subsequent courses (25% for KS patients).
Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.
Paediatric use: Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy.
Method of administration
Precautions to be taken before handling or administering the medicinal product.
The concentrate for solution for infusion must be diluted before use and should only be administered intravenously.
Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.

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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/mm3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm3.

WARNINGS & PRECAUTIONS
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving Paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and 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 doselimiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm3.
Frequent monitoring of blood counts should be instituted during Paclitaxel treatment. Patients should not be re-treated with subsequent cycles of Paclitaxel until neutrophils recover to a level 1500 cells/mm3 and platelets recover to a level > 100,000 cells/mm3.
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 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.

PREGNANCY AND LACTATION
Pregnancy
Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits.
There is no adequate data from the use of paclitaxel in pregnant women, however as with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women.
Paclitaxel 6 mg/ml Concentrate for Solution for Infusion should not be used during pregnancy unless the clinical condition of the woman requires treatment with paclitaxel.
Women of childbearing potential receiving paclitaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraception's for at least 6 months after treatment with paclitaxel.

Breast-feeding
It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breast-feeding should be discontinued for the duration of therapy with paclitaxel.

DRUG INTERACTIONS
Paclitaxel clearance is not affected by cimetidine premedication.
Cisplatin: Paclitaxel is recommended to be administered before cisplatin. When given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single agent use. Administration of paclitaxel after cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.
Doxorubicin: Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin.
Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours).
Active substances metabolised in the liver: The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

ADVERSE EFFECTS
The following side effects are common (occurring in greater than 30%) for patients taking Paclitaxel:
Low blood counts: Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding.
Hair loss: Arthralgias and myalgias, pain in the joints and muscles. Usually temporary occurring 2 to 3 days after Paclitaxel, and resolve within a few days.
Peripheral neuropathy (numbness and tingling of the hands and feet)
Nausea and vomiting (usually mild)
Diarrhea
Mouth sores
Hypersensitivity reaction. Fever, facial flushing, chills, shortness of breath, or hives after Paclitaxel is given (see allergic reaction). The majority of these reactions occur within the first 10 minutes of an infusion. Notify your healthcare provider immediately (premedication regimen has significantly decreased the incidence of this reaction).
The following are less common side effects (occurring in 10-29%) for patients receiving Paclitaxel:
Swelling of the feet or ankles (edema).
Increases in blood tests measuring liver function. These return to normal once treatment is discontinued.
Low blood pressure (occurring during the first 3 hours of infusion).
Darkening of the skin where previous radiation treatment has been given.
Nail changes (discoloration of nail beds - rare).

STORAGE: Store protected from light, at a temperature not exceeding 25°C.

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