75 mm

Paclitor® IV Injection

Paclitaxel USP Injection

DESCRIPTION

Paclitor® IV Injection is a preparation of Paclitaxel. 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 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.

MECHANISM OF ACTION

Paclitaxel is one of several cytoskeletal drugs that target tubulin. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division. Unlike other tubulin-targeting drugs such as colchicine that inhibit microtubule assembly, paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks the progression of mitosis and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division.

PHARMACOKINETIC PROPERTIES

Absorption: Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations.

The pharmacokinetics of paclitaxel were determined following 3- and 24-hour infusions at doses of 135 and 175 mg/m^2. The mean half-life was between 3.0 and 52.7 hours, and the mean non-compartmentally derived value for total body clearance was between 11.6 and 24.0 l/hr/m^2. The total body clearance appeared to decrease with higher plasma concentrations. The mean steady-state volume of distribution was between 198 and 688 l/m^2, indicating extensive extravascular distribution and/or tissue binding. Dose increases associated with the 3-hour infusion resulted in non-linear pharmacokinetics. When the dose increased by 30% from 135 mg/m^2 to 175 mg/m^2, the maximum plasma concentration (Cmax) increased by 75% and the area under the plasma concentration time curve (AUC0-∞) by 81%.

The variation of systemic paclitaxel exposure in the same patient was found to be minimal. No signs of cumulative effects were found for paclitaxel in association with multiple treatment courses.

Distribution: In vitro studies of serum protein binding indicate that 89-98% of paclitaxel is bound to proteins. Cimetidine, ranitidine, dexamethasone or diphenhydramine were not found to affect the protein binding of paclitaxel.

Biotransformation and elimination: The distribution and metabolism of paclitaxel in humans has not been fully investigated. The cumulative excretion of unchanged paclitaxel in the urine has been between 1.3% and 12.6% of the dose on average, which is an indication of extensive non-renal clearance. Hepatic metabolism and biliary clearance are possibly the principal mechanisms for elimination of paclitaxel. Paclitaxel is primarily metabolised by the action of CYP450 enzyme. An average of 26% of the radioactively marked dose of paclitaxel was eliminated in the faeces as a 6α-hydroxypaclitaxel, 2% as 3'p-dihydroxypaclitaxel and 6% as 6α-3'p-dihydroxypaclitaxel. 6 α-hydroxypaclitaxel is formed by the effect of CYP2C8, 3'p-hydroxypaclitaxel by CYP3A4 and 6α-3'p-dihydroxypaclitaxel by CYP2C8 and CYP3A4. The effect of renal or hepatic impairment on the elimination of paclitaxel after 3-hour infusions has not been studied. The pharmacokinetic parameters of a patient on haemodialysis were of values similar to those of non-dialysis patients when the administration rate was 135 mg/m^2 of paclitaxel as a 3-hour infusion.

Following an intravenous dose of 100 mg/m^2 given as a 3-hour infusion to 19 KS patients, the mean Cmax was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/m^2 (range 11-38) and the volume of distribution was 291 l/m^2 (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

In clinical trials where paclitaxel and doxorubicin were administered concomitantly, the distribution and elimination of doxorubicin and its metabolites were prolonged. Total plasma exposure to doxorubicin was 30% higher when paclitaxel immediately followed doxorubicin than when there was a 24-hour interval between drugs.

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.

DOSAGE AND ADMINISTRATION

Posology and method of administration

Posology

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	30 to 60 min
	50 mg IV	

* 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 3 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 intravenously 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 intravenously 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.

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.

CONTRAINDICATIONS

Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) (see section 4.4) or to any of the excipients. Paclitaxel is contraindicated during lactation. Paclitaxel should not be used in patients with baseline neutrophils <1.5 x 10^9/l (<1 x 10^9/l for KS patients) or platelets <100 x 10^9/l (<75 x 10^9/l for KS patients). In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections. Patients with severe hepatic impairment must not be treated with paclitaxel.

SIDE EFFECTS

- Bone Marrow: Neutropenia, Leukopenia, Thrombocytopenia, Anemia, Infections, Bleeding
- Hypersensitivity Reaction
- Abnormal ECG
- Peripheral Neuropathy
- Myalgia/Arthralgia
- Gastrointestinal: Nausea and vomiting, Diarrhea, Mucositis
- Alopecia
- Hepatic: Bilirubin elevations, Alkaline phosphatase elevations, AST (SGOT) elevations
- Injection Site Reaction

OVERDOSE

There is no known antidote for paclitaxel overdose. In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in paediatric patients may be associated with acute ethanol toxicity.

WARNING AND PRECAUTION

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

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

Patients must be pretreated with corticosteroids, diphenhydramine and H_2 antagonists.

Paclitaxel should be given before cisplatin when used in combination.

Significant hypersensitivity reactions, as characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in 2-4% of patients receiving paclitaxel in clinical trials. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with paclitaxel. Macrogolglycerol ricinoleate (polyoxyl castor oil), an excipient in this medicinal product, can cause these reactions.

Bone marrow suppression, primarily neutropenia, is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until the neutrophil count is ≥1.5 x 10^9/l (≥1 x 10^9/l for KS patients) and the platelets recover to ≥100 x 10^9/l (≥75 x 10^9/l for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital signs monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles).

Peripheral neuropathy: The occurrence of peripheral neuropathy is frequent; the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. In non-small cell lung cancer patients the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of single agent paclitaxel. In first-line ovarian cancer patients, administration of paclitaxel as a 3-hour infusion combined with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of a combination of cyclophosphamide and cisplatin.

Impaired hepatic function: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression. 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.

Ethanol: This product contains 49.7% vol ethanol (alcohol), i.e. up to 21 g per average dose, equivalent to 740 ml of a 3.5% vol beer, 190 ml of a 14% vol wine per dose. This may be harmful to patients suffering from alcoholism. It should also be taken into account when considering using this medicine in children and high risk groups such as those with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines.

Intra-arterial: Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal studies investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

Pseudomembranous colitis has also been reported, rarely, including cases in patients who have not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhoea occurring during or shortly after treatment with paclitaxel.

A combination of pulmonary radiotherapy and paclitaxel treatment (irrespective of the order of the treatments) may promote the development of interstitial pneumonitis.

Paclitaxel has been shown to be a teratogen, embryotoxic and a mutagen in several experimental systems. Therefore female and male patients of reproductive age must take contraceptive measures for themselves and/or their sexual partners during and for at least 6 months after therapy (see section 4.6). Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with paclitaxel.

In KS patients, severe mucositis is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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.

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.

Studies in KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

USE IN PREGNANCY AND LACTATION

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 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.

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

HANDLING AND DISPOSAL

The published guidelines related to procedures for the proper handling and disposal of cytotoxic medicines should be followed.

Care must be taken whenever handling cytotoxic products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

PREPARATION FOR INTRAVENOUS ADMINISTRATION

Paclitaxel Injection 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.

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. 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 Paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the Paclitaxel solution.

Stability

Unopened vials of 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.

PHARMACEUTICAL PRECAUTION

Store below 30 °C temperature. Keep away from light and wet place. Keep out of reach of children. Do not refrigerate.

PACKAGING

Paclitor® 30 IV Injection : Each box contains one multi-dose vial of Paclitaxel USP 30 mg/5 mL injection.

Paclitor® 100 IV Injection : Each box contains one multi-dose of vial Paclitaxel USP 100 mg/16.7 mL injection.

Paclitor® 300 IV Injection : Each box contains one multi-dose vial of Paclitaxel USP 300 mg/50 mL injection.

SK+F ONCOLOGY

Manufactured by
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