Paxel®

Paclitaxel USP

Presentation

Paxel® Injection 30 mg: Each vial contains 5 ml solution containing Paclitaxel USP 30 mg (6 mg/ml).
Paxel® Injection 100 mg: Each vial contains 16.7 ml solution containing Paclitaxel USP 100 mg (6 mg/ml).
Paxel® Injection 300 mg: Each vial contains 50 ml solution containing Paclitaxel USP 300 mg (6 mg/ml).

Description

Paxel® (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.

Pharmacokinetic Properties

Distribution:
Widely distributed into body fluids and tissues; affected by dose and duration of infusion one average, 89% of drugs is bound to serum protiens and the mean apparant volume of distribution at steady state, with 1 to 6 hour infusion: 67.1 L/m² and with the 24 houre infusion of Paxel® 30, ranged from 227-668 L/m²
Protein binding: 89% to 98%.
Metabolism: Hepatic via CYP2C8/9 and 3A4; forms metabolites
Half-life elimination:
1 to 6 hour infusion: Mean (beta): 6.4 hours
3 hour infusion: Mean (terminal): 13.1-20.2 hours
24-hour infusion: Mean (terminal):15.7-52.7 hours
Excretion: Feces (~70%, 5% as unchanged drug); urine (14%)
Clearance: Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 L/hour/m² ; After 24-hour infusions: 14.2-17.2 L/hour/m²

Clinical Information

Therapeutic Indications Ovarian Carcinoma
Paxel® is indicated as first line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first line therapy,Paxel is indicated in combination with cisplatin.
Breast carcinoma
Paxel® is indicated for the adjuvant treatment of node positive breast cancer administered sequentially to standarddoxorubicin-containing cpmbination chemotherapy.
Paxel® 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 anthracline unless clinically contraindicated.
Paxel® is indicated for the first line therapy of advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracline therapy is suitable or in combination with trastuzumab in patients who over express HER-2 at a 2+ or 3+ level as determined by immuno histochemistry.
Gemcitabine, in combination of Paxel®, is indicated in the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy.Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
Paxel® is indicated for the treatment of metastatic cancer of the breast,in combination with trastuzumab, in patients who have tumors that over-express HER-2 and who have not received previous chemotherapy for their metastatic disease.
Non Small Cell Lung Carcinoma
Paxel®, in combination with cisplatin,is indicated for the first line treatment of non small cell lung cancerin patients who are not candidates for potential curative surgery and/or radiation therapy.
Kaposi's Saocoma
Paxel® is indicated for the second line treatment of AIDS related Kaposi's Sarcoma.
Gastric Carcinoma
Paxel® is indicated for the treatment of Gastric Carcinoma

Dosage & Administration

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
Paxel® is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling Paxel®. The use of gloves is recommended. If Paxel® solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If Paxel® 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
Paxel® must be diluted prior to infusion. Paxel® 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. 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 anin-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. Paxel® 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. Paxel 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
- Paxel® 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 Paxel® 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, Paxel® has been use at several doses and schedules; however, the optimal regimem is not yet clear. The recommended regimen is Paxel® (paclitaxel) 135 mg/m² or175 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 3 hours every 2 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.

Gastric Cancer
- Once daily 210 mg/m² (Body surface area) by 3 houre 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)

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 level2.01-5 times ULN : 90 mg/m²
If transaminase levels 10 times ULN and bilirubin level >5 times ULN : Avoid use

Stability
Unopened vials of Paxel 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 Paxel 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.

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 Paxel® 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 arepolyethylene-lined) should be used.
Paclitaxel should be administered through I.V. tubing containing an in-line filter (with a microporous membrane not $> 0.22\mu$). 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.

Overdosage
There is no known antidote for Paclitaxel over dosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Side effects
Data given below is based on the polled 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.
Hematology
Bone marrow suppression is the major dose-limiting toxicity of Paclitaxel. Neutropenia, the most important hematologic toxicity, is dose and schedule dependent and is generally rapidly reversible. Neutropenia does not appear to increase with cumulative exposure and is neither more frequent nor more severe for patients previously treated with radiation therapy.The use of supportive therapy, including G-CSF, is recommended in case of severe neutropenia.12% of all treatment courses report fever. Thrombocytopenia is uncommon. Anemia (Hb<11 g/dl) is observed in 78% of all patients and is severe (Hb<8 g/dl) in 165 of the cases. No consistent relationship between dose or schedule and the frequency of anemia is observed.
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 anthracycline 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 arte 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-existingneuropathies 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/Genito-urinary
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 intestinal 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 arthalgia/myalgia, 8% experience severe symptoms.the symptoms are usually transient, occur 2-3 day after Paclitaxel administration and resolve within a few days .The frequently 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.

Contraindications
-Patients with a known hypersensitivity 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/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of < 1000 cells/mm^3.

Pregnancy and Lactation
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.
Severe hypersensitivity reactions have been reported; prolongation of the infusion (to 6 hours) plus premedication may minimize this effect. When administered as sequential infusions, taxane derivatives (docetaxel, Paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin) to limit myelosuppression. Elderly patients have an increased risk of toxicity (neutropenia, neuropathy).
Nursing Mothers
It is not known whether the drug is excreted in human milk. 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 Paxel® therapy.

Pediatric Use
The safety and effectiveness of 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 Paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m2 to 420 mg/m^2.The toxicity is most likely attributable to the high dose of the ethanol component of the Paclitaxel 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 Paclitaxel for use in this population.

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/m^2 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, nicardipine, NSAIDs, pioglitazone, and sulfonamides.

CYP3A4 inducers: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycins.

CYP3A4 inhibitors: May increase the levels/effects of paclitaxel. Example inhibitors include azole antifungals, ciprofloxacin, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, and verapamil.
Doxorubicin: Paclitaxel may increase doxorubicin levels/toxicity.

Storage conditions
Store at temperature not exceeding 25 °C in a dry place. Protect from light and moisture. Do not refrigerate.

Commercial pack
Paxel® Injection 30 mg: Each box contains one single-dose vial of 5 ml solution of Paclitaxel USP.
Paxel® Injection 100 mg: Each box contains one single-dose vial of 16.7 ml solution of Paclitaxel USP.
Paxel® Injection 300 mg: Each box contains one single-dose vial of 50 ml solution of Paclitaxel USP.

Medicine: Keep out of reach of children

For further information, please contact: 01977 157 108
(9.00 am - 5.00 pm)

Healthcare

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