For the use of Oncologist or a Hospital or a Laboratory. 8029616-9093

TORTAXEL (Paclitaxel Injection I.P.)

COMPOSITION

TORTAXEL 30

Each ml contains :

Paclitaxel I.P.	6 mg
Polyoxyl 35 Castor Oil I.P. (Cremophor ELP)	527 mg
Dehydrated Alcohol I.P.	49.7% v/v

TORTAXEL 100

Each ml contains :

Paclitaxel I.P.	6 mg
Polyoxyl 35 Castor Oil I.P. (Cremophor ELP)	527 mg
Dehydrated Alcohol I.P.	49.7% v/v

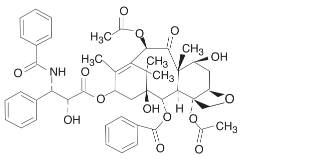
TORTAXEL 260

Each ml contains:

Paclitaxel I.P.	6 mg
Polyoxyl 35 Castor Oil I.P. (Cremophor ELP)	527 mg
Dehydrated Alcohol I.P.	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 5 β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one4,10-diacetate2-benzoate13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel has the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9.Paclitaxel has the following structural formula:



INDICATIONS

Paclitaxel is indicated as first-line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first-line therapy, is indicated in combination with cisplatin. Paclitaxel is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. Paclitaxel 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. Paclitaxel 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. Paclitaxel is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

CLINICAL PHARMACOLGICAL

Mechanism of Action

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers. It stabilizes microtubules by preventing depolymerization resulting in the inhibition of the normal dynamic reorganisation of the microtubule network essential for cellular functions. Paclitaxel also induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmocokinetics

The pharmcokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300mg/m^2, and infusion schedules, ranging from 3 to 24 hours and have been shown to be non-linear and saturable with a disproportionately large increase in C and AUC with max increasing dose accompanied by an apparent dose-related decrease in total body clearance.

Absorption

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. 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. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half life has ranged from 13.1 to 52.7 hours, and total body clearance has ranged from 12.2 to 23.8 L/h/m^2. Mean steady state volume of distribution has ranged from 198 to 688 L/m^2, indicating extensive extra-vascular distribution and/or tissue binding.

Distribution

On average, 89% of drug is bound to serum proteins; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of paclitaxel.

Metabolism

Paclitaxel metabolised primarily to 6á-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6á, 3'-pdihydroxypaclitaxel by CYP3A4.

Elimination

After intravenous administration of 15-275 mg/m^2 doses of Paclitaxel 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.

DOSAGE & 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. 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 administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

*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.

- Paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or
- Paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.

2) 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/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

*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 paclitaxel, at a dose of 175 mg/m^2 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, paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with **non-small cell lung carcinoma,** the recommended regimen, given every 3 weeks, is Paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2. For patients with **AIDS-related Kaposi's sarcoma,** paclitaxel administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m^2/week). In the 2 clinical trials evaluating these schedules, the former schedule (135 mg/m^2 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/m^2 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 20 mg PO);

2) Initiate or repeat treatment with paclitaxel only if the neutrophil count is at least 1000 cells/mm^3;

3) Reduce the dose of subsequent courses of paclitaxel by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 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 paclitaxel should not be repeated, until, the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

Paclitaxel 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/mm^3 for a week or longer) or severe peripheral neuropathy during paclitaxel therapy should have dosage reduced by 20% for subsequent courses of paclitaxel.The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Hepatic Impairment

Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Paclitaxel is not recommended in patients with severely 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. Paclitaxel is not recommended in patients with severely impaired hepatic function.

Preparation and Administration Precautions

Procedures for proper handling and disposal of anticancer drugs should be considered. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel Injection. If paclitaxel 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 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 extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Preparation for Intravenous Administration

TORTAXEL (Paclitaxel Injection I.P.) must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, I.P.; 5% Dextrose Injection, I.P.; 5% Dextrose and 0.9% Sodium Chloride Injection, I.P.; 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^{o}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 injection 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 Injection since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

CAUTIONS

The drug should be administered with caution in the following patients, Paclitaxel Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Patients receiving Paclitaxel Injection should be pretreated with corticosteroides, antihistamines, and H antagonists (such as dexamethasone, diphenhydramine and cimetidine or ranitidine) to minimize hypersensitivity reactions. Severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in patients receiving Paclitaxel Injection. These reactions are probably histamine mediated. One of these reactions was fatal in a patient treated without premedication. Patients who experiences sever hypersensitivity reactions to Paclitaxel Injection should not be rechallenged with the drug. Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted during Paclitaxel Injection treatment. Patients should not be treated with subsequent cycles of Paclitaxel Injection until neutrophils recover to a level > 1,500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

CONTRAINDICATION

- Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) 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 AIDS-related Kaposi's sarcoma (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.

WARNINGS AND PRECAUTIONS

WARNINGS

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer cytotoxic agents. Since significant hyper sensitivity reactions may occur, appropriate supportive equipment should be available. Patients must be pretreated with corticosteroids, antihistamines 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 reported in <1% of patients receiving paclitaxel after adequate premedication. 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 109/l (≥1 x 109/l for KS patients) and the platelets recover to ≥100 x 109/l (≥75 x 109/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

These have been reported rarely. 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 reported 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 reported 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 this combination, 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. Paclitaxel is not recommended in patients with severely impaired hepatic function. Since paclitaxel contains ethanol (396 mg/ml), consideration should be given to possible central nervous system and other effects. The amount of alcohol in this medicinal product may alter the effects of other medicines. 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

It 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. 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%.

PRECAUTIONS

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.

DRUG 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

Caution should be exercised during concurrent administration of active substances which are metabolised in the liver as such active substances may inhibit the metabolism of paclitaxel. The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 (CYP450) isoenzymes CYP2C8 and 3A4. Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, (to 6α-hydroxypaclitaxel) is the major metabolic pathway in humans. Based on current knowledge, clinically relevant interactions between paclitaxel and other CYP2C8 substrates are not anticipated. Concurrent administration of ketoconazole (a known potent inhibitor of CYP3A4) does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of interactions between paclitaxel and other CYP3A4 substrates/ inhibitors are limited. Therefore, caution should be

exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4. 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.

Hematology

Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel. Patients should not be re-treated with subsequent cycles of Paclitaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of Paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended. For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, Paclitaxel, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm^3.

Hypersensitivity Reaction

Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (eg, cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with Paclitaxel. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with Paclitaxel should be premedicated with corticosteroids (such as dexa-methasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of Paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with Paclitaxel.

Cardiovascular

Hypotension, bradycardia, and hypertension have been reported during administration of Paclitaxel, but generally do not require treatment. Occasionally Paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of Paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. When Paclitaxel is used in combination with doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Nervous System

Although the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of Paclitaxel. Paclitaxel contains dehydrated alcohol I.P., 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol.

Hepatic

There is limited evidence that the myelotoxicity of Paclitaxel may be exacerbated in patients with serum total bilirubin >2 times ULN. Extreme caution should be exercised when administering Paclitaxel to such patients, with dose reduction.

Injection Site Reaction

Injection site reactions, including reactions secondary to extravasation, were reported 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 Paclitaxel 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.

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 or the 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.

ADVERSE EFFECTS

The most frequent significant undesirable effect was bone marrow suppression. Severe neutropenia (< 0.5 x 10^9/l) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir < 50 x10^9/l at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb < 8.1 g/dl) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status. Neurotoxicity, mainly peripheral neuropathy, appeared to be more frequent and severe with a 175 mg/m^2 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m^2 24-hour infusion (25% peripheral neuropathy, 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy. Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients. A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy. Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. "recall", has been reported rarely. A specific treatment for extravasation reactions is unknown at this time. The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the postmarketing surveillance* of paclitaxel. The frequency of undesirable effects listed below is defined using the following convention:

Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations:	Very common: Infection Uncommon: Septic shock Rare*: Pneumonia, sepsis
Blood and the lymphatic system disorders:	Very common: Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia Rare: Febrile neutropenia Very rare*: Acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	Very common: Minor hypersensitivity reactions (mainly flushing and rash) Uncommon: Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills and back pains) Rare*: Anaphylactic reactions Very rare*: Anaphylatic shock
Metabolism and nutrition disorders:	Very rare*: Anorexia
Psychiatric disorders:	Very rare*: Confusional state
Nervous system disorders:	Very common: Neurotoxicity (mainly: peripheral neuropathy) Rare*: Motor neuropathy (with resultant minor distal weakness) Very rare* : Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia, neuroencephalopathy
Eye disorders:	Very rare*: Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended, optic nerve damage, Conjunctivitis, increased lacrimation, photopsia, visual floaters`
Ear and labyrinth disorders:	Very rare*: Ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders:	Common: Bradycardia Uncommon: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrio-ventricular block (may require pacemaker placement) and syncope, myocardial infarction Very rare*: Atrial fibrillation, supraventricular tachycardia, significant cardiovascular events, ventricular failure
Vascular disorders:	Very common: Hypotension Uncommon: Hypertension, thrombosis, thrombophlebitis, venous thrombosis Very rare*: Shock
Respiratory, thoracic and mediastinal disorders:	Rare*: Dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure Very rare*: Cough
Gastrointestinal disorders:	Very common: Nausea, vomiting, diarrhoea, mucosal inflammation Very rare*: Bowel obstruction, bowel perforation, ischaemic colitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, pancreatitis, Intestinal obstruction, intestinal perforation, Neutropenic enterocolitis (typhlitis)
Hepato-biliary disorders:	Very rare*: Hepatic necrosis, hepatic encephalopathy, cumulative hepatic toxicity
Skin and subcutaneous tissue disorders:	Very common: Alopecia Common: Transient and mild nail changes (changes in pigmentation or discoloration of nail bed) skin changes, Rare*: Pruritus, rash, erythema, tenderness, maculopapular rash Very rare*: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) Diffuse edema, thickening, and sclerosing of the skin
Musculoskeletal, connective tissue and bone disorders :	Very common: Arthralgia, myalgia
General disorders and administration site conditions:	Common: Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis) Rare*: Asthenia, pyrexia, dehydration, oedema, febrile reaction
Investigations:	Common: Severe elevation in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT)), severe elevation in alkaline phosphatase, ECG abnormality, premature beats, Uncommon: Severe elevation in bilirubin Rare*: Increase in blood creatinine

Breast cancer patients who received paclitaxel in the adjuvant setting following AC experienced more neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infection, fever, nausea/vomiting and diarrhoea than patients who received AC alone. However, the frequency of these events was consistent with the use of single agent paclitaxel, as reported above.

<u>Combination treatment</u>

Two major trials done for the first-line chemotherapy of ovarian carcinoma (paclitaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), and another investigating the combination with trastuzumab (planned subgroup analysis, paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (paclitaxel + cisplatin: over 360 patients). When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin. For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when paclitaxel (220 mg/m^2) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m^2) when compared to standard FAC therapy (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m^2) / doxorubicin (50 mg/m^2) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paclitaxel/doxorubicin arm. When paclitaxel was administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to paclitaxel or trastuzumab) were reported more frequently than with single agent paclitaxel: heart failure (8% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%), diarrhoea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel/trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single agent paclitaxel. Phase three Adjuvant breast carcinoma study revealed [Patients received 600 mg/m^2 cyclophosphamide and doxorubicin (AC) at doses of either 60 mg/m^2, 75 mg/m^2, or 90 mg/m^2 (with prophylactic G-CSF support and ciprofloxacin), every 3 weeks for 4 courses.] Compared to patients who received AC alone, patients who received AC followed by Paclitaxel experienced more Grade III/IV neurosensory toxicity, more Grade III/IV myalgia/arthralgia, more Grade III/IV neurologic pain (5% vs 1%), more Grade III/IV flu-like symptoms (5% vs 3%), and more Grade III/IV hyperglycemia (3% vs 1%). During the additional 4 courses of treatment with Paclitaxel, 2 deaths (0.1%) were attributed to treatment. During Paclitaxel treatment, Grade IV neutropenia was reported for 15% of patients, Grade II/III neurosensory toxicity for 15%, Grade II/III myalgias for 23%, and alopecia for 46%.When doxorubicin was administered in combination with paclitaxel in metastatic breast cancer, cardiac contraction abnormalities (20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. Congestive heart failure was observed in < 1% in both paclitaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paclitaxel single agent (New York Heart Association (NYHA) Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death. In all but these rare cases, patients responded to appropriate medical treatment. Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma: Except for haematologic and hepatic undesirable effects, the frequency and severity of undesirable effects are generally similar between KS patients and patients treated with paclitaxel monotherapy for other solid tumours, based on a clinical study including 107 patients. Blood and the lymphatic system disorders: Bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (<0.5 x 109/l) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for >7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting 7 days was 22%. Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal. Thrombocytopenia was observed in 50% of patients, and was severe (<50 x 109/l) in 9%. Only 14% experienced a drop in their platelet count <75 x 109/l, at least once while on treatment. Bleeding episodes related to paclitaxel were reported in <3% of patients, but the haemorrhagic episodes were localised. Anaemia (Hb <11 g/dl) was observed in 61% of patients and was severe (Hb <8 g/dl) in 10%. Red cell transfusions were required in 21% of patients. Platelet transfusion also required. Hepato-biliary disorders: Among patients (>50% on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

Opportunistic Infections: Cytomegalovirus, Herpes simplex, Pneumocystis carinii, M. avium intracellulare, Candidiasis, esophageal, Cryptosporidiosis, Cryptococcal meningitis, Leukoencephalopathy, other microorganism has been reported with treatment with paclitaxel.

Accidental Exposure : Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

USE IN PREGNANCY, CHILDREN AND GERIATRICS

PREGNANCY

Based on human experience, paclitaxel, is suspected to cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. 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. 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 have to use effective contraception during and up to 6 months after treatment.

LACTATION

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 Paclitaxel therapy.

CHILDREN

The safety and effectiveness of Paclitaxel in pediatric patients have not been established.Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy.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 350mg/m^2 to 420mg/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.

GERIATRIC

In clinical Studies, frequently severe myelosuppression, commonly severe neuropathy and higher incidence of cardiovascular events were reported in elderly patients.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 25^{o}C, Protected from light. Do not freeze.

Keep out of reach of children.

PRESENTATION

TORTAXEL (Paclitaxel Injection I.P.) is available in single dose vial containing Paclitaxel I.P. 30mg/5ml, 100mg/16.67ml, 260mg/43.34ml.

Marketed by :
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