℞ **PACLITERO 30/100/300**
Paclitaxel Injection 30 mg/100 mg/300 mg (6 mg/mL)

PACLITERO 30/100/300

Paclitaxel Injection 30 mg/100 mg/300 mg (6 mg/mL)

PACLITERO 30 (Paclitaxel Injection 30 mg/5 mL) (6 mg/mL)

Each mL contains 6 mg Paclitaxel USP.

PACLITERO 100 (Paclitaxel Injection 100 mg/16.7 mL) (6 mg/mL)

Each mL contains 6 mg Paclitaxel USP.

PACLITERO 300 (Paclitaxel injection 300 mg/50 mL (6 mg/mL) (6 mg/mL)

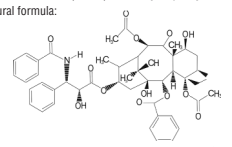
Each mL contains 6 mg Paclitaxel USP.

DESCRIPTION

Paclitaxel Injection is a clear colorless to slightly yellow viscous solution free form visible particles. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multi-dose vials. Each mL contains 6 mg paclitaxel USP., 527 mg of cremophor ELP, 0.497 mL Ethanol Anhydrous Ph.Eur and 2 mg of Anhydrous Citric acid Ph.Eur.

Paclitaxel is a natural product with anti-tumor activity. Paclitaxel is obtained via an extraction process from Taxus X media 'Hicksii'. The chemical name for paclitaxel is (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,-12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5H-cyclodeca [3,4] benz [1,2-b] oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at between 206.0°C and 216.0°C (With decomposition).

THERAPEUTIC INDICATIONS

Paclitaxel is indicated for the treatment of the following:

Ovarian Carcinoma

First-line therapy in combination with a platinum compound for the treatment of advanced metastatic carcinoma of the ovary. Second-line therapy for the treatment of advanced metastatic carcinoma of the ovary.

Breast Carcinoma

Adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy.

First-line therapy of advanced or metastatic breast cancer after relapse within 6 months of adjuvant therapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

First-line therapy of metastatic breast cancer in combination with trastuzumab in patients who over-express HER-2 as determined by immunohistochemistry.

First-line therapy of metastatic breast cancer in combination with an anthracycline in patients for whom anthracycline therapy is suitable.

Second-line therapy of advanced or metastatic breast cancer after failure of combination chemotherapy for metastatic disease. Prior therapy should have included an anthracycline unless clinically contraindicated.

Non-Small Cell Lung Carcinoma

First-line therapy in combination with a platinum compound or as a single agent for the treatment of non-small cell carcinoma of the lung in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Kaposi's Sarcoma

Second-line treatment of AIDS-related Kaposi's Sarcoma

POSOLOGY AND METHOD OF ADMINISTRATION

All patients must be premedicated prior to paclitaxel administration to reduce the risk of severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg orally (or its equivalent) approximately 12 and 6 hours before paclitaxel or 20mg I.V. approximately 30 to 60 minutes before paclitaxel, diphenhydramine 50 mg I.V. (or its equivalent) 30 to 60 minutes prior to paclitaxel and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes prior to paclitaxel.

Repeat courses of paclitaxel should not be administered to patients with solid tumours until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3 (<1000 cells/mm^3 for patients with Kaposi's sarcoma). Patients who experience severe neutropenia (<500 cells/mm^3) or severe peripheral neuropathy should receive a dosage reduced by 20% for subsequent courses. The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

Metastatic Carcinoma of the Ovary:

Combination therapy: For previously untreated patients, the recommended dosing regimen, given every 3 weeks, is paclitaxel administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by a platinum compound.

Alternatively, a more myelosuppressive regimen of paclitaxel may also be administered intravenously at a dose of 135 mg/m^2 over 24 hours followed by a platinum compound, every 3 weeks.

Single-agent therapy: In patients previously treated with chemotherapy the recommended regimen is 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

Carcinoma of the Breast:

Adjuvant therapy: Paclitaxel 175 mg/m^2 administered intravenously over 3 hours every 3 weeks for 4 courses sequentially to standard combination therapy.

Single-agent, first-line therapy after relapse within 6 months of adjuvant therapy: paclitaxel 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

Combination, first-line therapy of advanced or metastatic breast cancer: 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.

Combination, first-line therapy of metastatic breast cancer: In combination with doxorubicin (50 mg/m^2), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses.

Single-agent second-line therapy after failure of combination chemotherapy for metastatic disease: Paclitaxel 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

Non-Small Cell Lung Carcinoma:

Combination therapy: For previously untreated patients, the recommended dosing regimen given with a 3 week interval between courses is, paclitaxel 175 mg/m^2 administered intravenously over 3 hours followed by a platinum compound.

Alternatively, a more myelosuppressive regimen of paclitaxel may be administered intravenously 135 mg/m^2 over 24 hours followed by a platinum compound, with a 3 week interval between courses.

Single-agent therapy: Paclitaxel 175 to 225 mg/m^2 administered intravenously over 3 hours every 3 weeks.

AIDS-Related Kaposi's Sarcoma:

Second-line therapy: Paclitaxel 135 mg/m^2 administered intravenously over 3 hours with a 3 week interval between courses or 100mg/m^2 administered intravenously over 3 hours with a 2 week interval between courses (dose intensity 45-50 mg/m^2/week).

Based upon the immunosuppression observed in patients with advanced HIV disease, the following modifications are recommended in these patients.

1) the dose of dexamethasone as one of the three premedication drugs should be reduced to 10 mg orally
2) treatment with paclitaxel should be initiated or repeated only if the neutrophil count is at least 1000 cells/mm^3
3) the dose of subsequent courses of paclitaxel should be reduced by 20% for those patients who experience severe neutropenia (<500 cells/mm^3 for a week or longer)
4) concomitant hematopoietic growth factor (G-CSF), should be initiated as clinically indicated.

Hepatic Impairment

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Dose adjustment is recommended, as shown in Table 1 for both 3- and 24-hour infusions. Patients should be monitored closely for the development of profound myelosuppression. (See Pharmacological properties: Pharmacokinetic properties, Hepatic Impairment)

Table 1 Recommendations for Dosing in patients with Hepatic Impairment based on Clinical Trial Data

Degree of Hepatic Impairment			
Transaminase Levels		**Bilirubin Levels[a]**	**Recommended Paclitaxel Dose[b]**
24-hours infusion			
< 2 x ULN	and	≤ 1.5 mg/dL	135 mg/m^2
2 - < 10 x ULN	and	≤ 1.5 mg/dL	100 mg/m^2
< 10 x ULN	and	1.6 – 7.5 mg/dL	50 mg/m^2
≥ 10 x ULN	or	> 7.5 mg/dL	Not recommended
3-hour infusion			
< 10 x ULN	and	≤ 1.25 x ULN	175 mg/m^2
< 10 x ULN	and	1.26 - 2.0 x ULN	135 mg/m^2
< 10 x ULN	and	2.01 - 5.0 x ULN	90 mg/m^2
≥ 10 x ULN	or	> 5.0 x ULN	Not recommended

a Difference in criteria for bilirubin levels between the 3- and 24-hour infusion are due to difference in clinical trial design.

b Dosage recommendations are for the first course of therapy, further dose reduction in subsequent course should be based on individual tolerance.

ULN = Upper limit of normal.

Incompatibility

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. (See Special Instruction for Use, Handling and Disposal section.)

CONTRAINDICATIONS

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 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.

DRUG INTERACTIONS

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: Paclitaxel is recommended to be administered before cisplatin. When given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single agent use. Administration of paclitaxel after cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

Doxorubicin: Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin.

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. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, montelukast, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro.

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.

Epirubicin: Reports in the literature suggest that plasma levels of epirubicinol, a metabolite of epirubicin, may be increased when paclitaxel and epirubicin are used in combination. The clinical significance of the increased epirubicinol plasma levels is unknown.

Other Interactions

There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines

VACCINATIONS:

Concomitant use of paclitaxel with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defense mechanisms may be suppressed by paclitaxel. Vaccination with a live vaccine in a patient taking paclitaxel may result in severe infection. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought.

WARNINGS AND PRECAUTIONS

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

Paclitaxel should be administered as a diluted infusion.

Rare fatal reactions have occured in patients despite pre-treatment.

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, anti-histamines and H2 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 <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 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). In case of severe neutropenia (<500 cells/mm^3) during a course of paclitaxel, a 20% reduction in dose for subsequent courses of therapy is recommended.

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. In severe cases, paclitaxel infusions may need to be interrupted or discontinued at the discretion of the treating physician. 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). For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.

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. 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%.

Pediatric Use

The safety and effectiveness of paclitaxel in pediatric patients has 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/m^2 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.

Geriatric Use

Of 2228 patients who received paclitaxel in eight clinical studies evaluating its safety and efficacy in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older including

49 patients (1%) 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group."

PREGNANCY AND LACTATION

Pregnancy

Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits and to decrease fertility in rats.

There is no adequate data from the use of paclitaxel in pregnant women, however as with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women.

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion should not be used during pregnancy unless the clinical condition of the woman requires treatment with paclitaxel.

Women of childbearing potential receiving paclitaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraceptions for at least 6 months after treatment with paclitaxel.

Breast-feeding

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

Fertility

Paclitaxel has been shown to reduce fertility in rats.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

This medicinal product contains alcohol, which may impair the ability to drive or operate machines.

Consideration should also be given to possible CNS effects of premedications given to reduce the risk of severe hypersensitivity reactions.

SIDE EFFECTS

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in clinical studies. As the KS population is very specific, a special chapter based on a clinical study with 107 patients, is presented at the end of this section.

Size : 160 x 360 mm
Spec: 40-45 GSM Bible paper both side printing
Single Colour **Black**

The frequency and severity of undesirable effects, unless otherwise mentioned, are generally similar between patients receiving paclitaxel for the treatment of ovarian carcinoma, breast carcinoma, or NSCLC. None of the observed toxicities were clearly influenced by age.

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 x 10^9/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/m² 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m² 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. Paresthesia commonly occurs in the form of hyperesthesia. 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.

Rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

All patients received premedication prior to paclitaxel therapy. The frequency and severity of hypersensitivity reactions were not affected by the dose or schedule of paclitaxel administration. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia. Abdominal pain, pain in the extremities, diaphoresis, and hypertension are also noted.

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. Injection site 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, i.e. "recall", has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

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.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. ECG alterations in the form of repolarization abnormalities like sinus tachycardia, sinus bradycardia, and premature beats have been observed in clinical studies. Severe cardiac conduction abnormalities have been reported in <1% of patients during paclitaxel therapy. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with paclitaxel.

Gastrointestinal (GI) Toxicity: Mild to moderate nausea/vomiting, diarrhea and mucositis (also reported as pharyngitis or chelitis) were reported very commonly by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

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 post-marketing 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 (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome Uncommon: Septic shock Rare*: Pneumonia, peritonitis, sepsis
Blood and lymphatic system disorders:	Very common: Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding 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, back pain, chest pain, tachycardia, abdominal pain, pain in extremity, diaphoresis, and hypertension) Rare*: Anaphylactic reactions Very rare*: Anaphylactic shock
Metabolism and nutrition disorders:	Very rare*: Anorexia Not known*: Tumour lysis syndrome
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
Eye disorders:	Very rare*: Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended Not known*: Macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	Very rare*: Ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders:	Common: Bradycardia, Very common: abnormal ECG Uncommon: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrio-ventricular block and syncope, myocardial infarction Rare: Cardiac failure Very rare*: Atrial fibrillation, supraventricular tachycardia
Vascular disorders:	Very common: Hypotension Uncommon: Hypertension, thrombosis, thrombophlebitis Very rare*: Shock Not known*: Phlebitis
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 Rare*: Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis Very rare*: mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, oesophagitis, constipation, ascites
Hepato-biliary disorders:	Very rare*: Hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	Very common: Alopecia Common: Transient and mild nail and skin changes Rare*: Pruritus, rash, erythema Very rare*: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) Not known*: Scleroderma, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Very common: Arthralgia, myalgia Not known*: Systemic lupus erythematosus
General disorders and administration site conditions:	Common: Injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Rare*: Asthenia, pyrexia, dehydration, oedema, malaise
Investigations:	Common: Severe elevation in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT)), severe elevation in alkaline phosphatase 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.

Combination treatment

The following discussion refers to two major trials 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.

Cross-study comparison of neurotoxicity in CA139-209 and CA139-022 suggests that when paclitaxel is given in combinations with cisplatin 75 mg/m², the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m² given by 3-hour infusion (21%) than at a dose of 135 mg/m² given by 24-hour infusion (3%).

Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure during the combination therapy of paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

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/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m²) / doxorubicin (50 mg/m²) 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.

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 (seetrastuzumab Summary of Product Characteristics). 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 (see below), 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. However, patients with AIDS-related Kaposi's sarcoma may have more frequent and severe infections (including opportunistic infections*), and febrile neutropenia. These patients require a lower dose intensity and supportive care. Renal toxicity has a higher trend of incidence in KS patients as compared to patients with solid tumors.

*Opportunistic infections included cytomegalo virus, herpes simplex, Pneumocystis carinii, M. avium intracellulare, esophageal candidiasis, cryptosporidiosis, cryptococcal meningitis, and leukoencephalopathy."

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 10^9/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 10^9/l) in 9%. Only 14% experienced a drop in their platelet count <75 x 10^9/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.

Hepatobiliary 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.

"abnormal ECG", "cutaneous lupus erythematosus"

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties:

Pharmacotherapeutic group: Anti-neoplastic agent/taxanes

ATC code: L01C D01

Paclitaxel is an anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability inhibits the normal dynamic reorganisation of the microtubule network, which 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.

Pharmacokinetic Properties:

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/m². 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/m². The total body clearance appeared to decrease with higher plasma concentrations. The mean steady-state volume of distribution was between 198 and 688 l/m², 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/m² to 175 mg/m², the maximum plasma concentration (C_{max}) increased by 75% and the area under the plasma concentration time curve ($AUC_{0-\infty}$) 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.

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.

The distribution and metabolism of paclitaxel in humans has not been fully investigated. After intravenous administration of 15-275 mg/m² doses of paclitaxel as 1, 6, or 24-hour infusions, 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. In five patients administered a 225 or 250 mg/m² dose of radiolabeled paclitaxel as a 3-hour infusion, 14% of the radioactivity was recovered in the urine and 71% was excreted in the feces in 120 hours. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. 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. 6α-hydroxypaclitaxel is formed by the effect of CYP2C8, 3'p-hydroxypaclitaxel by CYP3A4 and 6α-3'p-dihydroxypaclitaxel by CYP2C8 and CYP3A4.

Special Populations

Renal Impairment

The effect of renal impairment on the disposition of paclitaxel has not been investigated.

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/m² of paclitaxel as a 3-hour infusion.

Hepatic Impairment

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin =2 times upper limit of normal (ULN) administered 175 mg/m² was increased, but with no apparent increase in the frequency or severity of toxicity. In five patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m²), but no observed increase in plasma exposure.

Following an intravenous dose of 100 mg/m² given as a 3-hour infusion to 19 KS patients, the mean C_{max} 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/m² (range 11-38) and the volume of distribution was 291 l/m² (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.

For use of paclitaxel in combination with other therapies, please consult the Summary of Product Characteristics of cisplatin, doxorubicin or trastuzumab for information on the use of these medicinal products.

SPECIAL INSTRUCTION FOR USE, HANDLING AND DISPOSAL

Paclitaxel is a cytotoxic anticancer drug and caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Following topical exposure, events have included tingling, burning and redness. 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 (See Warnings and Precautions section).

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Paclitaxel must be diluted prior to infusion to a final concentration of 0.3 to 1.2 mg/mL. Paclitaxel should be diluted in one of the following: 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following delivery of the solution through intravenous tubing containing an in-line 0.22 micron filter.

Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those that are polyethylene-lined, should be used. (See Incompatibilities.)

Diluted solutions are chemically and physically stable for up to 27 hours at temperature 25°C and room lighting conditions; infusions should be completed within this timeframe. There have been rare reports of precipitation with longer than the recommended 3-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

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.

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. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

HOW SUPPLIED

PACLITERO 30 (Paclitaxel Injection 30 mg/5 mL) (6 mg/mL)

Clear colorless to slightly yellow viscous solution free form visible particles

PACLITERO 100 (Paclitaxel Injection 100 mg/16.7 mL) (6 mg/mL)

Clear colorless to slightly yellow viscous solution free form visible particles

PACLITERO 300 (Paclitaxel Injection 300 mg/50 mL) (6 mg/mL)

Clear colorless to slightly yellow viscous solution free form visible particles

Pack Size: 1's count glass vial

"Not all presentations may be available locally".

STORAGE: Store below 30°C and Protect from light.

Product Owner:
HETERO LABS LIMITED
7-2-A2, Hetero Corporate,
Industrial Estates, Sanath nagar,
Hyderabad - 500 018

Manufactured by:
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