PACKAGE INSERT

(For the use of a Registered Medical Practitioner or a Hospital or Laboratory only.)

CYTAX 30/100/300
(Paclitaxel Injection USP 30 mg/5 ml, 100 mg/16.7 ml 300 mg/50 ml)

COMPOSITION:
Each ml contains:
Paclitaxel USP 6.0 mg
Dehydrated Alcohol BP 49.7% v/v
Polyoxyl 35 castor oil USNF q.s.

DESCRIPTION:
Paclitaxel for injection concentrate is a naturally occurring organic compound with a taxane ring, which has been demonstrated to possess anti-neoplastic property. Paclitaxel binds to microtubules and inhibits their depolymerisation into tubulin. Paclitaxel blocks a cell's ability to break down the mitotic spindles during mitosis, thereby preventing the cellular multiplication.

PRODUCT DESCRIPTION:
Paclitaxel for injection concentrate is a clear colourless to pale yellow solution, free from visible foreign material.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamics Properties:
Pharmacotherapeutic group: Antineoplastic agent/Taxanes; ATC Code: L01C D01.

Paclitaxel is an anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability inhibits normal dynamic reorganization 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 determined following 3 – and 24- hour infusion at doses of 135 and 175 mg/m^2. The mean half life was between 3.0 and 52.7 hours, and the mean non-compartmentally derived value for total body clearance was between 11.6 and 24.0 l/hr/m^2. The total body clearance appeared to decrease with higher plasma

concentrations. The mean steady-state volume of distribution was between 198 and 688 I/m^2, indicating extensive extravascular distribution and/or tissue binding. Dose increases associated with the 3-hour infusion resulted in non-linear pharmacokinetics. When the dose increased by 30% from 135 mg/m^2 to 175 mg/m^2, the maximum plasma concentration (Cmax) increased by 75% and the area under the plasma concentration time curve ($AUC_{0-\infty}$) by 81%.

The variation of systemic paclitaxel exposure in the same patients 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. The cumulative excretion of unchanged paclitaxel in the urine has been between 1.3% and 12.6% of the dose on average, which is an indication of extensive non-renal clearance. Hepatic metabolism and biliary clearance are possibly the principal mechanisms for elimination of paclitaxel. Paclitaxel is primarily metabolized 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. The effect of renal or hepatic insufficiency on the elimination of paclitaxel after 3-hour infusions has not been studied. The pharmacokinetic parameters of a patient on haemodialysis were of values similar to those of nondialysis patients when the administration rate was 135mg/m^2 of paclitaxel as a 3-hour infusion.

Following an intravenous dose of 100 mg/m^2 given as a 3-hour infusion to 19 KS patients; the mean C_{max} was 1530 ng/ml (range 761-2860 ng/ml) and the mean AUC 5619 ng.hr/ml (range 2609-9428 ng.hr/ml). Clearance was 20.6 l/h/m^2 (range 11-38) and the volume of distribution was 291 l/m^2 (range 121-638).

The terminal elimination half-life averaged 23.7 hours (range 12-33).

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

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.

INDICATIONS:

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 CYTAX 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 CYTAX or 20mg I.V. approximately 30 to 60 minutes before CYTAX, diphenhydramine 50 mg I.V. (or its equivalent) 30 to 60 minutes prior to CYTAX and cimetidine (300 mg) or ranitidine (50 mg) I.V. 30 to 60 minutes prior to CYTAX.

Repeat courses of CYTAX 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 CYTAX administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by a platinum compound.
Alternatively, a more myelosuppressive regimen of CYTAX 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: CYTAX 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: CYTAX 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 CYTAX is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. CYTAX 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), CYTAX should be administered 24 hours after doxorubicin. The recommended dose of CYTAX 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: CYTAX 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, CYTAX 175 mg/m^2 administered intravenously over 3 hours followed by a platinum compound.

Alternatively, a more myelosuppressive regimen of CYTAX 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: CYTAX 175 to 225 mg/m^2 administered intravenously over 3 hours every 3 weeks.

AIDS-Related Kaposi's Sarcoma:
Second-line therapy: CYTAX 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 CYTAX should be initiated or repeated only if the neutrophil count is at least 1000 cells/mm^3
3) the dose of subsequent courses of CYTAX 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.

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 CYTAX Dose[b]
		24-hour 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] Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.
[b] Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.
ULN = upper limit of normal.

Incompatibilities
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 TAXOL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Mode of Administration:
CYTAX® Injection USP Concentrate 6mg/ml is for IV use.

Contraindications:
Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to Paclitaxel, macroglycerol ricinoleate (polyoxyl castor oil) or to any of the excipients.

Paclitaxel is contraindicated during pregnancy and 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
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.

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, antihistamines and H2 antagonists. Paclitaxel should be given before cisplatin when used in combination.

Paclitaxel should be given before cisplatin when used in combination.

Significant hypersensitivity reactions:
As characterized by dyspnoea and hypotension requiring treatment, angioedema, and generalized 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. Macrogolycerol ricinoleate (polyoxyl castor oil), an excipients 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 re-treated until the neutrophil count is 1.5 x 10^9/l (1 x 10^9/l for KS patients) and the platelets recover to 100 x 10^9/l (75 x 10^9/l for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

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

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

When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with paclitaxel in this combination, they should undergo baseline assessment including history, physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan. Cardiac function should be further monitored during treatment (eg. 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 (eg. 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 111-1V myelosoppression. 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.

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.

Intraarterial: Special care should be taken to avoid intraarterial 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 diarrhea occurring during or shortly after treatment with paclitaxel.
A combination of pulmonary radiotherapy and paclitaxel treatment (irrespective of the order of the treatment) 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%.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Paclitaxel clearance is not affected by cimetidine premedication.

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

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

Active substance metabolized in the liver:
Caution should be exercised during concurrent administration of active substances which are metabolized 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 (eg: eryhthromycin, fluoxetine, gemfibrozil) or induce (eg 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.

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy:
Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits.

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

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

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

Breastfeeding:
It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breastfeeding 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

ADVERSE REACTIONS:
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 ($<0.5 \times 10^9$/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 $<50 \times 10^9$/l at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb <8.1g/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/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. 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 acontraindication 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 generalized urticaria) occurred in two (<1%) of 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 localized oedema, pain, erythema, and in duration 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 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 (1/1000, <1/100); rare (1/10000, <1/1000); very rare (<1/10000)

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 leukemia, myelodysplastic syndrome
Metabolism and nutrition disorders	Very rare*: Anorexia
Psychiatric disorders	Very rare*: Confusional stage
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 recommanded
Ear and labyrinth disorders	Very rare*: Ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders	Common: Bradycardia Uncommon: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block and syncope, myocardial infarction Very rare*: Atrial fibrillation, supraventricular tachycardia
Vascular disorders	Very common: Hypotension Uncommon: Hypertension, thrombosis, thrombophlebitis Very rare*: Shock
Respiratory, thoracic and mediastinal disorders	Rare*: Dyspnoea, plueral 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
Hepato-biliary disorders	Very rare*: Hepatic necrosis, hepatic encephalopathy
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) Musculoskeletal, connective tissue Very common: Arthralgia, myalgia
Musculoskeletal, connective tissue and bone disorders	Very common: Arthralgia, myalgia
General disorders administration site conditions	Common: Injection site reactions (including localized oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis) Rare*: Asthenia, pyrexia, dehydration, oedema
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 111 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 111 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 cyclosphosphamide followed by cisplatin.

For the first-line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever and diarrhea were reported more frequently and with severity when paclitaxel (220 mg/m^2) was administered as a 3-

hour infusion 24 hours following doxorubicin (50mg/ 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 metastastic 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%), arthalgia (37% vs 21%), tachycardia (125 vs 4%), diarrhea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 35%), 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 15%). Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel/trastuzumab combination vs single agent pacliatxel. Severe events were reported at similar rates for paclitaxel/traztuzumab and single agent paclitaxel.

When doxorubicin was administered in combination 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 1/11 10% vs 0%: NYHA Class 111/1V 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 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 > 7days 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 x109/l, at least once while on treatment. Bleeding episodes related to paclitaxel were reported in <3% of patients, but the haemorrhagic episodes were localized.

Anaemia (HB <11 g/dl) was observed in 61% of patients and was severe (Hb<8 g/dl) in 10%. Red cell transfusion were required in 21% of patients.

Hepato-biliary disorders:
Among patients > 50% on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phophatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

OVERDOSE:
There is no known antidote for Paclitaxel overdose. The primary anticipated complications of overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:

Handling: Paclitaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling paclitaxel. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. Contact of paclitaxel with skin and mucous membranes should be avoided.

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, dyspnoea, chest pain, burning throat, and nausea have been reported.

Preparation for IV administration: During dilution of the concentrate for infusion, cytostatic dispensing needles or similar devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the solution.

Prior to infusion, paclitaxel must be diluted to a ready-to-use solution for infusion (0.3 to 1.2 mg/ml) using aseptic techniques with one of the following solutions:

• 9 mg/ml (0.9%) sodium chloride solution for infusion
• 50 mg/ml (5%) glucose solution for infusion
• 50 mg/ml glucose and 9 mg/ml sodium chloride solution for infusion, or
• Ringer's solution containing 50 mg/ml glucose

Once diluted, the ready-to-use infusions are for single use only.

The ready-to-use infusion should be visually inspected for particulate matter and discoloration. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. However haziness does not affect the potency of the product. **The solution for infusion should be administered through an in-line filter with microporous membrane not greater than 0.22 microns.** No significant losses in potency have been noted following simulated delivery of the solution through I.V tubing containing an in-line (0.22 micron) filter.

There have been some reports of precipitation during paclitaxel infusions, with precipitation usually taking place towards the end of a 24-hour infusion period. To reduce the risk of precipitation, paclitaxel should be used as soon as possible after dilution and excessive shaking or agitation should be avoided. The infusion solution should be regularly inspected during infusion and the infusion should be discontinued if precipitation occurs.

To minimize patient exposure to DEHP which may be leached from plasticized PVC infusion bags, sets, or other medical instruments, diluted paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (Polypropylene, polyolefin) and administered through polyethylene-lined administrations sets. Use of filter devices which incorporate short inlet and/or outlet plasticized PVC tubing has not resulted in significant leaching of DEHP.

Disposal: All items used for preparation, administration, infusion or otherwise coming into contact with paclitaxel should be placed in an appropriate safety container and disposed according to local guidelines for the handling of cytotoxic compounds.

STORAGE:
Store the vials in the original cartons below 30°C & protect from light.
CYTAX® injection once diluted, the ready-to-use infusions are for single use only and not for multiple use.

If it is not using immediately after dilution, it remain stable physically, microbiologically & chemically up to 27 hours with storage at 15–25°C.

LIST OF EXCIPIENTS
Ethanol anhydrous
Polyoxyl 35 castor oil
Sodium metabisulphite
Water for Injection

Nitrogen

DOSAGE FORMS AND PACKAGING AVAILABLE
Paclitaxel Injection USP 30 mg/5 ml, 100 mg/16.7 ml and 300 mg/50 ml are packed as 1 vial per carton.

Packing details for 30 mg/5 ml pack:
Primary packaging material
1. 5 ml clear tubular vial USP type I
2. 20 mm Fluoro tec closer greyepprs1/4A siliconized
Secondary packaging material
1. 20 mm opaque light blue flip off Aluminium seal

Packing details for 100 mg/16.7 ml pack:

Primary packaging material
1. 20 ml clear tubular vial USP type I
2. 20 mm Fluoro tec closer greyepprs1/4A siliconized
Secondary packaging material
1. 20 mm opaque light blue flip off Aluminium seal

Packing details for 300 mg/50 ml pack:

Primary packaging material
1. 50 ml clear tubular vial USP type I
2. 20 mm Fluoro tec closer greyepprs1/4A siliconized
Secondary packaging material
1. 20 mm opaque light blue flip off Aluminium seal

NAME AND ADDRESS OF MANUFACTURER

Manufactured by:

Intas Pharmaceuticals Limited.
Plot No. 457-458, Village Matoda, Bavla Road,
And Plot no: 191/218 P, Village: Chacharwadi,
Ta-Sanand, Dist. - Ahmedabad.