

UNITAXEL Inj. 100 mg/ 16.67 mL

Concentrate for Solution

for Infusion



Paclitaxel 100 mg

ROUTE OF ADMINISTRATION : For Intravenous use

COMPOSITION	
Each vial (16.67 mL) contains	
Paclitaxel	100 mg

Excipients :
Povidone, Polyoxyl 35 Caster Oil, Polysorbate 80, Polyethylene Glycol 400, Malic Acid, Dehydrated Alcohol

DESCRIPTION
After opening before dilution : Colorless to pale yellow viscous liquid in an amber vial
After dilution : Colorless to pale yellow viscous liquid

PHARMACODYNAMICS
Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

PHARMACOKINETICS
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. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 11.6 to 24.0 l/hr/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion, increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135 mg/m² to 175 mg/m², the Cmax and AUC_{0-∞} values increased 75% and 81%, respectively.
Inpatient variability in systemic paclitaxel exposure was minimal. There was no evidence for accumulation of paclitaxel with multiple treatment courses.
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 Cancer
In first line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced disease or a residual disease > 1cm after initial laparotomy, in combination with cisplatin.
In second line chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum based therapy.
Breast Cancer
In the adjuvant setting, paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.
Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.
As a single agent, treatment of metastatic carcinoma of the breast in patients who have failed to respond adequately to standard treatment with anthracyclines or in whom anthracycline therapy has not been appropriate.

Advanced non-small cell lung cancer (NSCLC)
Paclitaxel, in combination with cisplatin, is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgical intervention and/or radiation therapy.
AIDS-related Kaposi's sarcoma (KS)
Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Paclitaxel should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.
All patients must be premedicated with corticosteroids, antihistamines, and H₂ antagonists prior to Paclitaxel 6 mg/ml, concentrate for solution for infusion, e.g.

Medicinal product	Dose	Administration prior to Paclitaxel
dexamethasone	20 mg oral* or IV	For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min
diphenhydramine**	50 mg IV	30 to 60 min
cimetidine or ranitidine	300 mg IV 50 mg IV	30 to 60 min

*8–20 mg for KS patients
** or an equivalent antihistamine e.g. chlorpheniramine

First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of paclitaxel and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel are recommended: paclitaxel 175 mg/m² administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m² every three weeks or paclitaxel 135 mg/m², in a 24-hour infusion, followed by cisplatin 75 mg/m², with a 3 week interval between courses.
Second-line chemotherapy of ovarian carcinoma: the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3 week interval between courses.
Adjuvant chemotherapy in breast carcinoma: the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.
First-line chemotherapy of breast carcinoma: when used in combination with doxorubicin (50 mg/m²), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m² administered intravenously over a period of 3 hours, with a 3-week interval between courses. When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m² 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 (for detailed trastuzumab posology see the Summary of Product Characteristics of Herceptin®).
Second-line chemotherapy of breast carcinoma: the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, with a 3-week interval between courses.
The treatment of advanced non-small-cell lung carcinoma (NSCLC): the recommended dose of paclitaxel is 175 mg/m² administered over a period of 3 hours, followed by cisplatin 80 mg/m², with a 3 week interval between courses.
The treatment of AIDS-related KS: the recommended dose of paclitaxel is 100 mg/m² administered as a 3-hour intravenous infusion every two weeks.
Subsequent doses of paclitaxel should be administered according to individual patient tolerance.
Paclitaxel should not be readministered until the neutrophil count is $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for KS patients) and the platelet count is $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for KS patients). Patients who experience severe neutropenia (neutrophil count < 500/mm³ for a week or longer) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients).
Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment should not be treated with paclitaxel.
Paediatric population
Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy
Method of administration
Precautions to be taken before handling or administering the medicinal product
The concentrate for solution for infusion must be diluted before use and should only be administered intravenously. Paclitaxel should be administered intravenously through an in-line filter with a microporous membrane $\leq 0.22 \mu\text{m}$.

CONTRAINDICATIONS
Paclitaxel is contraindicated in patients with severe hypersensitivity to paclitaxel or to any excipients listed in excipients especially polyoxyethylated 35 castor oil.
Paclitaxel should not be used in patients with baseline neutrophils < 1,500/mm³ (< 1,000/mm³ for KS patients) at the start of therapy.
Paclitaxel is contraindicated during lactation.
In KS, Paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections

WARNINGS AND PRECAUTIONS
Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
Given the possibility of extravasation, close monitoring of the infusion site for possible infiltration during administration of the drug is recommended.
Patients must be pretreated with corticosteroids, antihistamines and H₂ antagonists.
Paclitaxel should be given before cisplatin when used in combination.
Significant hypersensitivity reactions 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 the medicinal product.
Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for KS patients) and platelets recover to $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for KS patients).
Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 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. 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.
No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment must not be treated with paclitaxel.

Severe cardiac conduction abnormalities have been reported rarely with single agent paclitaxel. If patients develop significant cardiac 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 sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian carcinoma.
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, ECG, echocardiogram, and/or 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/m²) 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).

Although 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) for all subsequent courses of paclitaxel is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by cisplatin.
Special care should be taken to avoid intra-arterial application of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.
Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of *interstitial pneumonitis*.
Since paclitaxel concentrate for solution for infusion contains anhydrous ethanol (391 mg/ml), consideration should be given to possible CNS and other effects.
Paclitaxel concentrate for solution for infusion contains Polyoxyl 35 Castor oil, which may cause severe allergic reactions.
Pseudomembranous colitis has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.
In KS patients, **severe mucositis** is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%
Paclitaxel has shown to be teratogenic, embryotoxic and mutagenic in many experimental systems.
Therefore sexually active fertile female and male patients should use effective methods of contraception during treatment and up to six months after treatment for men and women. Hormonal contraception is contraindicated in hormone receptor positive tumors.

DRUG INTERACTION
The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given before cisplatin. When paclitaxel is given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single-agent use. When paclitaxel was given after cisplatin, patients showed a more profound myelosuppression and an approximately 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.
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.
The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and neflavinir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

PREGNANCY AND LACTATION
There are no studies in pregnant women. Paclitaxel has been shown to be embryo- and fetotoxic in rabbits and to decrease fertility in rats. Paclitaxel should not be administered to nursing mothers.
If Paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Paclitaxel.

ADVERSE EFFECTS
The frequency and severity of adverse reactions, 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.
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.
The most frequent significant adverse reaction was **bone marrow suppression**. Severe neutropenia (< 500 cells/mm³) 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 < 50,000/mm³ at least once while on study. **Anaemia** was observed in 64% of patients, but was severe (Hb < 5 mmol/l) 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. 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.
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. 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. Alopecia: Alopecia was observed in 87% of patients and was abrupt in onset. Pronounced hair loss of ≥50% is expected for the majority of patients who experience alopecia. Disseminated intravascular coagulation (DIC), often in association with sepsis or multi-organ failure, has been reported. The table below lists adverse reactions associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting.

System Organ Class	Frequency /Adverse Reactions
Infections and infestations:	Very common: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome Uncommon: septic shock Rare*: sepsis, peritonitis, pneumonia Very rare*: Pseudomembranous colitis
Blood and the lymphatic system disorders:	Very common: myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding Rare*: febrile neutropenia Very rare*:acute myeloid leukaemia, myelodysplastic syndrome Not known: disseminated intravascular coagulation
Immune system disorders:	Very common: minor hypersensitivity reactions (mainly excessive 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 extremities, diaphoresis and hypertension) Rare*: anaphylactic reactions Very rare*: anaphylactic shock Not known*: Bronchospasm
Metabolism and nutrition disorders:	Rare*: Dehydration 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*: grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache
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*: hearing loss, ototoxicity, tinnitus, vertigo
Cardiac disorders:	Common: bradycardia Uncommon: myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy Rare: heart failure Very rare*: atrial fibrillation, supraventricular tachycardia
Vascular disorders:	Very common: hypotension Uncommon: thrombosis, hypertension, thrombophlebitis Very rare*: shock Not known*: phlebitis
Respiratory, thoracic and mediastinal disorders:	Rare*: respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion Very rare*: cough
Gastrointestinal disorders:	Very common: diarrhoea, vomiting, nausea Rare*: bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis Very rare*: mesenteric thrombosis, neutropenic colitis, ascites, oesophagitis, constipation
Hepatobiliary 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
Musculoskeletal and connective tissue disorders:	Very common: arthralgia, myalgia Not known*: systemic lupus erythematosus, scleroderma
General disorders and administration site conditions:	Very common: Mucosal inflammation Common: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Rare*: pyrexia, asthenia, oedema, malaise
Investigations:	Common: severe elevation in AST (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

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/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 (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab 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
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 (< 500 cells/mm³) 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 (< 50,000 cells/mm³) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm³, 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. **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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that the formulation contains alcohol. The ability to drive or to use machines may be decreased due to alcohol content of this medicinal product.

OVERDOSE

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

INCOMPATIBILITIES

Polyoxoethylated 35 castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels, which increase with time and concentration. Consequently, the preparation, storage and administration of diluted paclitaxel should be carried out using non-PVC-containing equipment.

INSTRUCTION OF USE

Preparation for IV administration: prior to infusion, Paclitaxel concentrate for solution for infusion must be diluted using aseptic techniques in 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection, to a final concentration of 0.3 to 1.2 mg/ml.

The product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 27 hours in 0.9% sodium chloride solution, 5% glucose solution, a mixture of 0.9% sodium chloride and 5% glucose solution, or Ringer's solution containing 5% glucose at temperature below 30° C.

STORAGE

Preserve in hermetic containers, protected from light. Store at temperature below 30° C.

SHELF LIFE

Unopened vial
24 months

PACKAGE

1 Vial/Box

Revised in 29-April-2019



Product registration holder: Eucogen Pharma Sdn. Bhd., 6A, Jalan Sungai Burung U 32/U, Bukit Rimau, Seksyen 32, 40460 Shah Alam, Selangor, Malaysia.