320 x 235 mm

45gsm with fold

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: Palmar-plantar erythrodysesthesia syndrome
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: Asthenia, pyrexia, 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

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 (New York Heart Association (NYHA) Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death. In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy. AIDS-related Kaposi's sarcoma

Except for haematologic and hepatic undesirable effects (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.

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.

A15. Symptoms and Treatment of 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.

A16. Effects on ability to drive and use machines

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

A17. Preclinical Safety Data

Not applicable

A18. Instructions for Use Incompatibilities

Macrogolglycerol ricinoleate (polyoxyl castor oil) can result in di-(2-ethylhexyl)phthalate [DEHP] leaching from plasticized polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage, and administration of paclitaxel should be carried out in non-PVC-containing equipment such as glass, polypropylene, or polyolefin.

Disposal & 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:
- 0.9% Sodium Chloride Injection
- 5% Dextrose Injection
- 5% Dextrose & 0.9% Sodium Chloride Injection
- 5% Dextrose in Ringer's 24 hr Injection

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

Protection instructions for preparation of Paclitaxel solution for infusion

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available, mouth cover and goggles should be used.
2. Pregnant women or women who may become pregnant, should not handle this product.
3. Opened containers, like injection vials and infusion bottles and used canules, syringes, catheters, tubes, and residuals of cytostatics should be considered as HAZARDOUS WASTE and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
4. Follow the instructions below in case of spillage:
- protective clothing should be worn
- broken glass should be collected and placed in the container for HAZARDOUS WASTE.
- contaminated surfaces should be flushed properly with copious amounts of cold water.
- the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE.
5. In the event of paclitaxel contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
6. In case of contact of paclitaxel with eyes, wash them thoroughly with plenty of cold water. Contact an ophthalmologist immediately.

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

A19. Storage Conditions

Unopened vial

Store below 30ºC. Protect from light.

After Dilution:

After dilution chemical and physical in-use stability has been demonstrated for:

Diluent	Target Concentration	Storage Conditions	Time period
0.9% Sodium Chloride Injection	0.3 mg/ml and 1.2 mg/ml	Room temperature (25°C±2°C)	24 hr
5% Dextrose Injection	0.3 mg/ml and 1.2 mg/ml	Room temperature (25°C±2°C)	24 hr
5% Dextrose & 0.9% Sodium Chloride Injection	0.3 mg/ml and 1.2 mg/ml	Room temperature (25°C±2°C)	24 hr
5% Dextrose in Ringer's Injection	0.3 mg/ml and 1.2 mg/ml	Room temperature (25°C±2°C)	24 hr

From a microbiological point of view, the diluted 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 normally not be longer than 24 hours at Room temperature (25°C±2°C), unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

After opening before dilution: After first use and following multiple needle entries and product withdrawals, any unused concentrate maintains microbial, chemical and physical stability when stored below 25°C, protected from light for up to 28 days. Other in-use storage times and conditions are the responsibility of the user.

A20. Shelf Life

Product Condition	Shelf Life
Unopened vial	24 months
After opening before dilution	28 days at room temperature (25°C±2°C)
After Dilution	24 hr at room temperature (25°C±2°C)

A21. ATC Code

Pharmacotherapeutic group: Antineoplastic agent/taxanes

ATC code: L01C D01

Nature and contents of container:

Paxol-Paclitaxel Concentrate for solution for infusion 6mg/ml-30mg/5ml is filled in 5ml molded clear glass vial type-I with reinforced Non-PVC Base which are stoppered with 20mm Fluro coated rubber stopper and tampered with 20mm Aluminium flip off seal. Each vial is packed into secondary carton along with a package insert.

Paxol-Paclitaxel Concentrate for solution for infusion 6mg/ml-100mg/16.7ml is filled in 20ml molded clear glass vial type-I with reinforced Non-PVC Base which are stoppered with 20mm Fluro coated rubber stopper and tampered with 20mm Aluminium flip off seal. Each vial is packed into secondary carton along with a package insert.

Paxol-Paclitaxel Concentrate for solution for infusion 6mg/ml-260mg/43.4ml is filled in 50ml molded clear glass vial type-I with reinforced Non-PVC Base which are stoppered with 20mm Fluro coated rubber stopper and tampered with 20mm Aluminium flip off seal. Each vial is packed into secondary carton along with a package insert.

Paxol-Paclitaxel Concentrate for solution for infusion 6mg/ml-300mg/50ml is filled in 50ml molded clear glass vial type-I with reinforced Non-PVC Base which are stoppered with 20mm Fluro coated rubber stopper and tampered with 20mm Aluminium flip off seal. Each vial is packed into secondary carton along with a package insert.

Date of revision of package insert: 15.02.2022

MAL No. : MAL22046023AZ

Product Registration Holder:
Unimed Sdn Bhd
53, Jalan Tembaga SD 5/2B, Bandar Sri
Damansara, 52200, Kuala Lumpur, Malaysia

Manufactured by :
VENUS REMEDIES LIMITED
Hill Top Industrial Estate, Jharmajri, EPIP,
Phase-I (Extn.), Bhatoli Kalan, Baddi,
Distt. Solan, Himachal Pradesh, 173205, India

B81/PX30/4779, B81/PX100/4780, B81/PX260/4781, B81/PX300/4782

VENUS® Enjoy Innovations

To be sold by retail on the prescription of an Oncologist/Cancer Hospital/Institution only

Paxol
Paclitaxel Concentrate for Solution for Infusion

A1. Product Name :
Paxol (Paclitaxel Concentrate for Solution for Infusion 6 mg/ml)

A2. Name and Strength of Active Ingredient (s)
Active ingredient:
Paclitaxel USP
Strength: 30 mg/5 ml, 100 mg/16.7 ml, 260 mg/43.4 ml & 300 mg/50 ml

Composition:
Paxol 30 mg/5 ml
Each ml contains:
Paclitaxel USP 6 mg
Polyoxyl 35 Castor Oil USNF 527 mg
Dehydrated Alcohol USP 49.7% v/v

Paxol 100 mg/16.7 ml
Each ml contains:
Paclitaxel USP 6 mg
Polyoxyl 35 Castor Oil USNF 527 mg
Dehydrated Alcohol USP 49.7% v/v

Paxol 260 mg/43.4 ml
Each ml contains:
Paclitaxel USP 6 mg
Polyoxyl 35 Castor Oil USNF 527 mg
Dehydrated Alcohol USP 49.7% v/v

Paxol 300 mg/50 ml
Each ml contains:
Paclitaxel USP 6 mg
Polyoxyl 35 Castor Oil USNF 527 mg
Dehydrated Alcohol USP 49.7% v/v

A3. Dosage Form:
Concentrate for Solution for Infusion.

A4. Product Description:
Unopened vial: A clear colorless to pale yellow solution free from visible extraneous particulate matter filled in Type-I glass vial with rubber plug and flip off seal.
After Dilution: Clear solution (after dilution in 5.0% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, 5.0% Dextrose Injection and 0.9% Sodium Chloride Injection USP, 5% Dextrose in Ringer's Injection)

A5. Pharmacodynamics:
Pharmacotherapeutic group: Antineoplastic agent/taxanes ATC code: L01C D01

Mechanism of action

Paclitaxel is an antimicrotubule 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.

A6. Pharmacokinetics:

Absorption 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 (AUC0-∞) 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.

Distribution *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.

Biotransformation and elimination 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 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. The effect of renal or hepatic impairment 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 non-dialysis patients when the administration rate was 135 mg/m² of paclitaxel as a 3-hour infusion.

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.

A7. Indication:

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 receptor 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.

A8. Recommended Dose:

Posology

Pre-medication: All patients must be given pre-medication consisting of corticosteroids, antihistamines and H_2-receptor antagonists prior to paclitaxel administration, in order to prevent severe hypersensitivity reactions. Such pre-medication may consist of:

Table 1: Pre-medication Schedule

Pre-medication	Dose	Administration Priorto Paclitaxel
Dexamethasone	20 mg oral* or IV**	Oral: Approx. 12 and 6 hours IV: 30 – 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
** intravenous
***or an equivalent antihistamine e.g. chlorphenamine 10 mg IV, administered 30 to 60 minutes prior to paclitaxel

Paclitaxel should be administered using an in-line filter with a microporous membrane of ≤0.22 microns.

Given the possibility of extravasation, it is advisable to monitor closely the infusion site for possible infiltration during administration

First-line treatment of ovarian cancer: Although alternative medication regimens for paclitaxel are under investigation at present, a combination therapy of paclitaxel and cisplatin is recommended.

Depending on the duration of infusion, two different dosages are recommended for paclitaxel treatment: 175 mg/m² of paclitaxel is administered as an intravenous infusion over a period of three hours followed thereafter by 75 mg/m² of cisplatin and the therapy is repeated at 3-week intervals, or 135 mg/m² of paclitaxel is administered as an intravenous infusion over a period of 24 hours followed thereafter by 75 mg/m² of cisplatin and the therapy is repeated at 3-week intervals.

Second-line treatment of ovarian cancer: The recommended dose of paclitaxel is 175 mg/m² administered over 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.

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.

Advanced non-small cell lung cancer: The recommended dose of paclitaxel is 175 mg/m2 administered over 3 hours followed by 80 mg/m² of cisplatin, with a 3-week interval between courses.

Treatment of AIDS-related KS: The recommended dose of paclitaxel is 100 mg/m² administered as a 3- hour intravenous infusion every two weeks.

Dose adjustment: Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be re-administered until the neutrophil count is ≥1.5 x 10^9/l (≥1 x 10^9/l for KS patients) and the platelet count is ≥100 x 10^9/l (≥75 x 10_9/l for KS patients).

Patients who experience severe neutropenia (neutrophil count <0.5 x 10^9/l for a minimum of 7 days) 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 must not be treated with paclitaxel.

Paediatric use: 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.

A9. Route of Administration:

Paclitaxel is administered by intravenous infusion.

A10. Contraindication:

Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) or to any of the excipients used in the formulation of Paclitaxel Concentrate for solution for Infusion.

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.

A11. Warning 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, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists. Paclitaxel should be given before cisplatin when used in combination.

Significant hypersensitivity reactions, as characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have 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).

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 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/ 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).

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%.

A12. Interaction With Other Medicaments:

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: Paclitaxel is recommended to be administered b efore cisplatin. When given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single agent use. Administration of paclitaxel a fter 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.

Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours).

Active substances *metabolised in the liver:* 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 nelfinavir) 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.

A13. 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.

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.

A14. Side Effects:

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 and as reported in the post-marketing surveillance of paclitaxel.

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 Very rare: Pseudomembranous colitis
Blood and 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 (DIC)
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 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: 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 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 Rare: Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis Very rare: mesenteric thrombosis, neutropenic colitis, oesophagitis, constipation, ascites