For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Paclitaxel Injection USP (150 mg/25 ml)

PACLITAX

Composition
Each ml contains
Paclitaxel USP ..... 6 mg
Dehydrated alcohol BP 49.7%v/v
Anhydrous citric acid BP..... q.s.
Polyoxyl 35 castor oil USNF ..... q.s.

Excipients with effects: castor oil, ethanol

Dosage Form
Injection

Pharmacology

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.

Clinical efficacy and safety
In first-line treatment of ovarian cancer, the safety and efficacy of paclitaxel were evaluated in two major randomised controlled trials (compared with cyclophosphamide 750 mg/m² + cisplatin 75 mg/m² therapy).

In the Intergroup trial (BMS CA 139-209), over 650 patients with stage II_{b-c}, III or IV primary ovarian cancer had administered to them a maximum of 9 courses of treatment with paclitaxel (175 mg/m² over a 3-hour period) followed by cisplatin (75 mg/m²) or control treatment. In another major study (GOG 111/B-MS CA139-022), a maximum of 6 courses of treatment with paclitaxel were administered (135 mg/m², during a 24-hour infusion) combined with cisplatin (75 mg/m²) or control treatment; the trial involved over 400 patients with stage III or IV primary ovarian cancer with a > 1 cm residual tumour after staging laparotomy, or with distant metastases. While the two different posologies were not compared with each other directly, in both trials the patients on paclitaxel and cisplatin had a significantly higher response rate, later onset of progression of disease and longer survival time than the patients on standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion of paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p = 0.0014), and a significant reduction of 19% in the risk of death (p = 0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/ unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m² following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006) ; paclitaxel treatment was associated with a reduction in the risk of death of 7% (95%CI: 0.78-1.12). All subset analyses favoured the paclitaxel arm. In this study patients with hormone receptor positive tumor had a reduction in the risk of disease recurrence of 23% (95%CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95%CI: 0.7-1.11).

In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.

In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by paclitaxel (220 mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of paclitaxel/doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second study, the efficacy and safety of the paclitaxel and trastuzumab combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m²) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m²) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the paclitaxel/trastuzumab combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to paclitaxel alone. The most significant toxicity observed with the paclitaxel/trastuzumab combination was cardiac dysfunction *(see Undesirable effects)*.

In the treatment of very advanced non-small cell lung cancer, the combination of 175 mg/m² of paclitaxel and 80 mg/m² of cisplatin (given after paclitaxel) has been studied in two phase III trials (367 patients on paclitaxel therapy). Both trials were randomised. In one of the trials the control group received cisplatin (100 mg/m²) and in another, 100 mg/m² of teniposide followed thereafter by 80 mg/m² of cisplatin (367 patients in the control group). The results of both trials were similar. There were no significant differences between the paclitaxel therapy and control therapy regarding mortality, primary end event (the median survival time in the paclitaxel groups were 8.1 and 9.5 months, and in the control groups 8.6 and 9.9 months). There were no significant differences in the median time of progression of the disease between the therapies either. The benefit was significant regarding clinical response. Studies on the quality of life indicate that the lack of appetite caused by combination treatment containing paclitaxel is smaller, but they also indicate an increased incidence of peripheral neuropathy (p<0.008) with combination treatment.

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines. This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (confidence interval (CI) 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent after the first 3 cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least 2 months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-not estimable). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.

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 ($AUC_{0-\infty}$) by 81%.

The variation of systemic paclitaxel exposure in the same patient was found to be minimal. No signs of cumulative effects were found for paclitaxel in association with multiple treatment courses.

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 6 α-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.

Following an intravenous dose of 100 mg/m² given as a 3-hour infusion to 19 KS patients, the mean C_{max} was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/m² (range 11-38) and the volume of distribution was 291 l/m² (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 - 33).

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

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

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 receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable *(see Warning and Precautions and Pharmacodynamics)*

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.

Limited efficacy data supports this indication; a summary of the relevant studies is shown in *see Pharmacodynamics.*

Dosage and Method of Administration
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 Prior to 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 *(see Pharmacodynamics).*

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 *(see Drug interaction and Pharmacodynamics).*

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) *(see Warning and Precautions).*

Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see *Warning and Precautions and Pharmacokinetics).* 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 *(see Storage and other handling)* and should only be administered intravenously.

Contraindications
Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) *(see Warning and Precautions*) or to any of the excipients.

Paclitaxel is contraindicated during lactation *(see Fertility, 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.

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, 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 *(see Dosage and administration).*

Paclitaxel should be given before cisplatin when used in combination *(see Drug interaction).*

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). *For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.*

Peripheral neuropathy: The occurrence of peripheral neuropathy is frequent; the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of paclitaxel. In non-small cell lung cancer patients the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of single agent paclitaxel. In first-line ovarian cancer patients, administration of paclitaxel as a 3-hour infusion combined with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of a combination of cyclophosphamide and cisplatin.

Impaired hepatic function: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression *(see Dosage and administration).* Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments *(see Pharmacodymanics).* 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 *(see Fertility, pregnancy and lactation).* 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%.

Drug Interactions
Paclitaxel clearance is not affected by cimetidine premedication.

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

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

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

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

Studies in KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paclitaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

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.

Lactation
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 *(see Contraindications)*.

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.

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

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

The most frequent significant undesirable effect was **bone marrow suppression**. Severe neutropenia (<0.5 x 10^9/l) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir <50 x 10^9/l at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb <8.1 g/dl) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly **peripheral neuropathy**, appeared to be more frequent and severe with a 175 mg/m² 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m² 24-hour infusion (25% peripheral neuropathy, 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Arthralgia or **myalgia** affected 60% of patients and was severe in 13% of patients.

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. "recall", has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

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.

The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the post-marketing surveillance* of paclitaxel.

The frequency of undesirable effects listed below is defined using the following convention:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations:	Very common: Infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome Uncommon: Septic shock Rare*: Pneumonia, peritonitis, sepsis 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
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
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)
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
The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (paclitaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), and another investigating the combination with trastuzumab (planned subgroup analysis, paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (paclitaxel + cisplatin: over 360 patients) *(see Pharmacokinetics)*.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

Incompatibility
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.

Shelf-Life
24 months

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

Diluent	Target Concentration	Storage Conditions	Time period
0.9% (9 mg/ml) sodium chloride solution for infusion	0.3 mg/ml and 1.2 mg/ml	2-8°C in the absence of light in non-PVC (polyolefin) infusion bags	28 days
5% (50 mg/ml) glucose solution for infusion	0.3 mg/ml and 1.2 mg/ml	2-8°C in the absence of light in non-PVC (polyolefin) infusion bags	14 days
0.9% (9 mg/ml) sodium chloride solution for infusion	0.3 mg/ml and 1.2 mg/ml	25°C under normal lighting conditions in non-PVC (polyolefin) infusion bags	72 hours
5% (50 mg/ml) glucose solution for infusion	0.3 mg/ml and 1.2 mg/ml	25°C under normal lighting conditions in non-PVC (polyolefin) infusion bags	72 hours
5% (50 mg/ml) glucose and 0.9% (9 mg/ml) sodium chloride solution for infusion	0.3 mg/ml and 1.2 mg/ml	25°C under normal lighting conditions in non-PVC (polyolefin) infusion bags	72 hours
Ringer's solution containing 5% (50 mg/ml) glucose	0.3 mg/ml and 1.2 mg/ml	25°C under normal lighting conditions in non-PVC (polyolefin) infusion bags	72 hours

Although this product contains ethanol, it cannot be considered as assurance of microbiological integrity.

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 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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.

Storage & Handling Instructions
Store at a temperature not exceeding 25°C. Store in the original package to protect from light. Paclitaxel injection is physico-chemically stable up to 28 days once opened at 25°C.

Freezing does not have an adverse effect on the preparation. Refrigerated product may precipitate but will re-dissolve on reaching room temperature with little or no agitation. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

After first use or after dilution, see Shelf-life.

Handling instruction
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.

Storage of the ready-to-use infusion see shelf-life.

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 minimise patient exposure to DEHP which may be leached from plasticised 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 administration sets. Use of filter devices which incorporate short inlet and/or outlet plasticised 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.

Presentation
PACLITAX Carton containing vial of 25 ml

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