SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel ADVAGEN Concentrate for Solution for Infusion 6 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 6 mg paclitaxel.
Each vial of 5 ml contains 30 mg of paclitaxel.
Each vial of 16.7 ml contains 100 mg of paclitaxel.
Each vial of 50 ml contains 300 mg of paclitaxel.

Excipient(s) with known effect:
Ethanol 392 mg/ml
Polyoxyethylated 35 castor oil (Macrogolglycerol ricinoleate 35) 527mg/ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
A clear, colourless to slightly yellow viscous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paclitaxel 6 mg/ml concentrate for solution for infusion is indicated for the treatment of the following:

Ovarian carcinoma:

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

Breast carcinoma:

- Adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy.
- First-line therapy of advanced or metastatic breast cancer after relapse within 6 months of adjuvant therapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- First-line therapy of metastatic breast cancer in combination with trastuzumab in patients who over-express HER-2 as determined by immunohistochemistry.
- First-line therapy of metastatic breast cancer in combination with an anthracycline in patients for whom anthracycline therapy is suitable.
- Second-line therapy of advanced or metastatic breast cancer after failure of combination chemotherapy for metastatic disease. Prior therapy should have included an anthracycline unless clinically contraindicated.

Non-small cell lung carcinoma:

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

Kaposi's sarcoma:

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

4.2 Posology and method of administration

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

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

Metastatic Carcinoma of the Ovary:

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

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

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

Carcinoma of the Breast:

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

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

Combination, first-line therapy of advanced or metastatic breast cancer: In combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3- week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

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

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

Non-Small Cell Lung Carcinoma:

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

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

Single-agent therapy: Paclitaxel 175 to 225 mg/m2 administered intravenously over 3 hours every 3 weeks.

AIDS-Related Kaposi's Sarcoma:

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

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

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

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

Table 1 Recommendations for Dosing in Patients with Hepatic Impairment Based on Clinical Trial Data

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

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

Incompatibilities

Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. (See **Special Instruction for Use, Handling and Disposal** section.)

Special Instruction for Use, Handling and Disposal

Paclitaxel is a cytotoxic anticancer drug and caution should be exercised in handling paclitaxel. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Following topical exposure, events have included tingling, burning and redness. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Injection Site Reaction** section).

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

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

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

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

Diluted solutions are chemically and physically stable for up to 27 hours at temperature between 15°C to 30°C and room lighting conditions; infusions should be completed within this timeframe. There have been rare reports of precipitation with longer than the recommended 3-hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

Devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

Procedures for proper handling and disposal of anticancer drugs should be considered.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing paclitaxel. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, especially Polyoxyethylated 35 castor oil (Macrogolglycerol ricinoleate 35) (see section 4.4).Lactation (see section 4.6).
Patients with baseline neutrophils < 1,500/mm³ (<1,000/mm³ for KS patients).
In KS, patients with concurrent, serious, uncontrolled infections.

4.4 Special warnings and precautions for use

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.

Paclitaxel should be administered as a diluted infusion. Patients must be pretreated with corticosteroids, antihistamines and H_2-antagonists (see section 4.2).

Paclitaxel should be given before cisplatin when used in combination (see section 4.5).

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 drug.

Bone marrow suppression (primarily neutropenia) is dose and schedule dependent and is the principal dose limiting toxicity within a regimen. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500cells/mm^3 (<1,000 cells/mm^3 for patients with Kaposi's Sarcoma). In case of severe neutropenia (<500 cells/mm^3) during a course of paclitaxel, a 20% reduction in dose for subsequent courses of therapy is recommended. (See **POSOLOGY AND ADMINISTRATION** section.)

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Dose adjustment is recommended. Patients should be monitored closely for the development of profound myelosuppression (see section 4.2).

No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should 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. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel is used in combination with doxorubucin 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). For more details see Package Insert of trastuzumab or doxorubicin.

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.

Others
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 *ethanol* (392 mg/ml), consideration should be given to possible CNS and other effects.

Paclitaxel concentrate for solution for infusion contains Polyoxyl 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.

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 (see section 4.6). Hormonal contraception is contraindicated in hormone receptor positive tumors.

Geriatric Use
Of 2228 patients who received paclitaxel in eight clinical studies evaluating its safety and efficacy in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older including 49 patients (1%) 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group.

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

4.5 Interaction with other medicinal products and other forms of 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 gynaecological 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 (see section 5.2).

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

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6α- hydroxypaclitaxel, is the major metabolic pathway in humans. 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 drug 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 CYP3A4.

Paclitaxel clearance is not affected by cimetidine premedication.

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.

4.6 Fertility, pregnancy, and lactation

Pregnancy
There is no adequate information on the use of paclitaxel in pregnant women. Paclitaxel has been shown to be embryotoxic and foetotoxic in rabbits, and to decrease fertility in rats.
As with other cytotoxic drugs, paclitaxel may cause foetal harm, and is therefore contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with paclitaxel, 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
Paclitaxel is contraindicated during lactation (see section 4.3). It is not known whether paclitaxel is excreted in human milk. Breastfeeding should be discontinued for the duration of therapy.

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.

4.7 Effects on ability to drive and use machines

Since paclitaxel contains ethanol, consideration should be given to the possibility of CNS and other effects. Consideration should also be given to possible CNS effects of premedications given to reduce the risk of severe hypersensitivity reactions.

4.8 Undesirable effects

The frequency and severity of adverse events are generally similar between patients receiving paclitaxel for treatment of ovarian, breast, non-small cell lung carcinoma, or Kaposi's Sarcoma (KS). However, patients with AIDS-related Kaposi's sarcoma may have more frequent and severehematologic toxicity, infections (including opportunistic infections*), and febrile neutropenia. These patients require a lower dose intensity and supportive care. Elevated liver function tests and renal toxicity have a higher trend of incidence in KS patients as compared to patients with solid tumors.

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

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies
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 administered as one of two doses (135 or 175 mg/m^2) and one of two schedules (3 or 24 hours) in the metastatic setting.

Hematologic Toxicities: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (<500 cells/mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Infectious episodes occurred very commonly and were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm^3 at least once while on treatment; 7% had a platelet count <50,000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel dose and schedule.

Neurologic: In general, the frequency and severity of neurologic manifestations were dose dependent in patients receiving single-agent paclitaxel. The frequency of peripheral neuropathy increased with cumulative dose. Paresthesia commonly occurs in the form of hyperesthesia. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. 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.

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

Hypersensitivity Reactions (HSR): All patients received premedication prior to paclitaxel therapy. The frequency and severity of HSR were not affected by the dose or schedule of paclitaxel administration. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia. Abdominal pain, pain in the extremities, diaphoresis, and

hypertension are also noted. Minor hypersensitivity reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paclitaxel therapy.

Injection Site Reactions: During intravenous administration, injection site reactions were usually mild and consisted of localised edema, pain, erythema, tenderness, and induration; on occasion, extravasationcan result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

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

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

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

Unless otherwise noted, the table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel (812 patients treated in clinical studies) or as reported in the postmarketing surveillance* of paclitaxel.

The frequency of undesirable effects listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Infections and infestations:	*Very common*: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome *Common:* flu syndrome *Uncommon:* septic shock *Rare*:* pneumonia, peritonitis, sepsis
Blood and lymphatic system disorders:	*Very common*: myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding *Common:* neutropenic fever *Uncommon:* severe anaemia *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 extremities, diaphoresis and hypertension) *Rare*:* anaphylactic reactions *Very rare**: anaphylatic shock
Metabolism and nutrition disorders:	*Uncommon**: weight gain, weight loss *Very rare**: anorexia *Not known**: tumour lysis syndrome
Psychiatric disorders:	*Very rare**: confusional stage
Nervous system disorders:	*Very common*: neurotoxicity (mainly: peripheral neuropathy) , paraesthesia, somnolence *Common:* depression, severe neuropathy, nervousness, insomnia, hypokinesia, abnormal gait, abnormal thinking, hypoaesthesia, taste change *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:	*Uncommon:* dry eyes, amblyopia, visual field defect *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:	*Very common:* Abnormal ECG *Common:* bradycardia , tachycardia, palpitation, syncope *Uncommon*: cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction , congestive heart failure *Rare**: cardiac failure *Very rare**: atrial fibrillation, supraventricular tachycardia
Vascular disorders:	*Very common*: hypotension *Common:* vasodilatation (flushing) *Uncommon:* hypertension, thrombosis, thrombophlebitis *Very rare**: shock *Not known*:* phlebitis
Respiratory, thoracic and mediastinal disorders:	*Common:* epistaxis *Rare*:* dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure *Very rare**: cough , pulmonary hypertension
Gastrointestinal disorders:	*Very common*: nausea, vomiting, diarrhoea, mucosal inflammation , stomatitis, abdominal pain *Common:* dry mouth, mouth ulceration, melaena, dyspepsia *Rare*:* bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis *Very rare**: mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis
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 *Uncommon:* changes in nail pigmentation or discoloration of nail bed *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) , folliculitis *Not known**: scleroderma, cutaneous lupus erthematosus
Musculoskeletal, connective tissue disorders:	*Very common:* arthralgia, myalgia *Common:* bone pain, leg cramps, myasthenia, back pain *Not known*:* systemic lupus erythematosus
General disorders and administration site conditions:	*Very common:* asthenia, pain, oedema including peripheral and face *Common*: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) , chest pain, chills *Rare*:* asthenia, pyrexia, dehydration, oedema, malaise
Renal and urinary disorders	*Common:* dysuria
Investigations:	*Common*: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase *Uncommon:* severe elevation in bilirubin *Rare**: increase in blood creatinine

Adverse Event Experiences from Studies with Combination Treatment

The following discussion refers to previously untreated patients with ovarian carcinoma or NSCLC who received paclitaxel in combination with cisplatin, patients with inoperable NSCLC who received single-agent paclitaxel in combination with Best Supportive Care, patients with breast cancer who received paclitaxel after doxorubicin/cyclophosphamide in the adjuvant setting, patients with metastatic breast cancer who received paclitaxel as first-line therapy with trastuzumab, and patients with AIDS-related Kaposi's sarcoma. In addition, rare events that have been reported from postmarketing experience or from other clinical studies are described.

Paclitaxel + Cisplatin
When administered as a 3-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 3-hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

Cross-study comparison of neurotoxicity in CA139-209 and CA139-022 suggests that when paclitaxel is given in combinations with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m^2 given by 3-hour infusion (21%) than at a dose of 135 mg/m^2 given by 24-hour infusion (3%).

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

Paclitaxel + Trastuzumab
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, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis, and injection site reaction. Some of these frequency differences may be due to the increased number and duration oftreatments with paclitaxel/trastuzumab combination vs single agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single agent paclitaxel.

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 and rarely has been associated with death. In all but these rare cases, patients responded to appropriate medical treatment.

Paclitaxel + Doxorubicin
Congestive heart failure has been reported for combination therapy of paclitaxel and doxorubicin in previously untreated patients with metastatic breast carcinoma and no prior chemotherapy.

Cases of myocardial infarction have been reported rarely. Cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure have been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Paclitaxel + Radiotherapy
Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

4.9 Overdose

There is no known antidote for paclitaxel overdosage.

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.

5. CLINICAL PHARMACOLOGY

5.1 Mechanism of Action

Paclitaxel is a novel 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of paclitaxel have been evaluated over a wide range of doses, up to 300 mg/m^2, andinfusion schedules, ranging from 3 to 24 hours and have been shown to be non-linear and saturable with a disproportionately large increase in Cmax and AUC with increasing dose accompanied by an apparent doserelated decrease in total body clearance.

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 13.1 to 52.7 hours, and total body clearance has ranged from 12.2 to 23.8 L/h/m^2. Mean steady state volume of distribution has ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding.

Variability in systemic paclitaxel exposure, as measured by AUC (0-∞) for successive treatment courses is minimal; there is no evidence of accumulation of paclitaxel with multiple treatment courses.

Distribution
On average, 89% of drug is bound to serum proteins; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3- p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (See **INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** section).

Excretion
After intravenous administration of 15-275 mg/m^2 doses of paclitaxel as 1, 6, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose. This indicates extensive non-renal clearance of paclitaxel. In five patients administered a 225 or 250 mg/m^2 dose of radiolabeled paclitaxel as a 3-hour infusion, 14% of the radioactivity was recovered in the urine and 71% was excreted in the feces in 120 hours. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance.

Special Populations

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

Hepatic Impairment
The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤2 times upper limit of normal (ULN) administered 175 mg/m^2 was increased, but with no apparent increase in the frequency or severity of toxicity. In five patients with serum total bilirubin >2 times ULN, there was a statistically nonsignificant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m^2), but no observed increase in plasma exposure. (See **POSOLOGY AND ADMINISTRATION: Hepatic Impairment** section and **SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Hepatic Impairment** section.)

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel is a potential carcinogenic and genotoxic agent, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be mutagenic in both in vitro and in vivo mammalian test systems.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol anhydrous
Chromatographically purified polyoxyl 35 castor oil (Macrogolglycerol ricinoleate 35)

6.2 Incompatibilities

Polyoxyethylated 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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before opening:
Refer to outer carton for expiration date.

After opening before dilution:
Chemical and physical in-use stability has been demonstrated for 28 days at 25°C following multiple needle entries and product withdrawals. From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

After dilution:
After dilution the solution is for single use only.
Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2°C to 8°C and at 25°C for 7 days when diluted in 5% dextrose solution, 5% dextrose and 0.9% sodium chloride solution and for 14 days when diluted in 0.9% sodium chloride injection.

From a microbiological point of view, 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 normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Vial *before opening:*
Store below 30°C. Store in the original package in order to protect from light.

After opening before dilution:
Do not store above 25°C. Store in the original package in order to protect from light.

Diluted solutions: See section 6.3.

6.5 Nature and contents of container

- 1x5ml Type I glass vial (closed with 13 mm fluororesin laminated chlorobutyl rubber stopper and an aluminium shell with a green plastic flip-off tear-off seal) contains 30 mg of Paclitaxel in 5 ml.
- 1x16.7ml Type I glass vial (closed with 20 mm fluororesin laminated chlorobutyl rubber stopper and an aluminium shell with an orange plastic flip-off tear-off seal) contains 100mg of Paclitaxel in 16.7 ml.
- 1x50ml Type I glass vial (closed with 20 mm fluororesin laminated chlorobutyl rubber stopper and an aluminium shell with a red plastic flip-off tear-off seal) contains 300mg of Paclitaxel in 50 ml.

The vials are packaged individually in a carton.

Not all pack sizes may be marketed.

7. PRODUCT OWNER

ADVAGEN Pte Ltd
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Singapore 408564

8. DATE OF REVISION OF THE TEXT

28 Feb 2023