1. NAME OF THE MEDICINAL PRODUCT
Ebetaxel Injection 6 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active: Each ml contains 6 mg Paclitaxel.
Inactive: Each mL contains absolute ethanol 402 mg, polyoxyl castor oil 522 mg.
Molecular formula: $C_{47}H_{51}NO_{14}$
Molecular weight: 853.9
CAS: 33069-62-4

Paclitaxel is a natural product with antitumour activity. It is a white to off-white crystalline powder that is extremely highly lipophilic and practically insoluble in water.
Paclitaxel is partially soluble in ethanol and is therefore formulated with polyoxyl castor oil and absolute ethanol.
Ebetaxel Injection is supplied as a clear, colourless to pale yellow solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Ovarian Carcinoma
- First-line therapy in combination with a platinum compound for the treatment of advanced metastatic carcinoma of the ovary.
- Second-line therapy for the treatment of advanced metastatic carcinoma of the ovary.

Breast Carcinoma
- Adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy.
- First-line therapy of advanced or metastatic breast cancer after relapse within 6 months of adjuvant therapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- First-line therapy of metastatic breast cancer in combination with trastuzumab in patients who overexpress 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 unsuitable.
- 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 20 mg I.V. approximately 30 to 60 minutes before paclitaxel, diphenyhydramine 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 1,500 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/m^2 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 100 mg/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.

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 paclitaxel solutions with plasticized polyvinyl chloride (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 anti-cancer 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, dyspnoea, 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.

Dilution should be carried out under aseptic conditions by trained personnel in a designated area. **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, and is not removed by filtration. Paclitaxel should be administered through an in-line filter with a microporous membrane ≤0.22 µm. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line 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**.)

After the final dilution of Ebetaxel Injection Concentrate, the bottle should be swirled gently to disperse the paclitaxel. Do not shake. After dilution the solution is for single use only.

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.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2 to 8°C for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal ofcytotoxic drugs (see **Handling and disposal** below). Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

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.

Handling and disposal
The published guidelines related to procedures for the proper handling and disposal of cytotoxic drugs should be followed.

4.3 Contraindications
Patients is contraindicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or polyoxyl castor oil.

Paclitaxel should not be administered to patients with solid tumours who have baseline neutrophil counts of <1,500 cells/mm^3 or in patients with AIDS-related Kaposi's Sarcoma with baseline or subsequent neutrophil counts of <1000 cells/mm^3 (See **Posology and Method of Administration** section).

4.4 Special warnings and precautions for use
General
Paclitaxel should be administered under the supervision of medical staff/ physician experienced in the use of cancer chemotherapeutic agents.

Paclitaxel **s**hould be administered as a diluted infusion. Patients must be treated with corticosteroids, antihistamines, and H_2 antagonists before receiving paclitaxel. (See **Posology and Method of Administration** section).

Paclitaxel should be given before a platinum compound when it is given in combination with a platinum compound.

Anaphylaxis and Severe Hypersensitivity Reactions
Anaphylaxis and severe hypersensitivity reactions have occurred commonly in patients receiving paclitaxel. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pre-treatment. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See **Posology and Method of Administration** section.) In case of a severe hypersensitivity reaction, paclitaxel infusion should be discontinued immediately and the patient should not be retreated with paclitaxel. (See **Undesirable Effects** section.)

Hematologic Toxicity
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 1,500 cells/mm^3 (<1,000 cells/mm^3 for patients with Kaposi's Sarcoma). In cases 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 Method of Administration** section.)

Cardiovascular Toxicity
Hypotension, hypertension and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. In severe cases, paclitaxel infusions may need to be interrupted or discontinued at the discretion of the treating physician. Frequent monitoring of vital signs, particularly during the first hour of paclitaxel infusion is recommended. Continuous electrocardiographic monitoring is not required except for patients with serious conduction abnormalities. When paclitaxel is used in combination with trastuzumab or

doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. (See **Undesirable Effects** section.)

Nervous system
The occurrence of peripheral neuropathy is frequent, but usually not severe. A dose reduction of 20% for subsequent courses of paclitaxel is recommended for severe neuropathy. Paclitaxel contains dehydrated ethanol. Consideration should be given to possible central nervous system (CNS) and other effects of ethanol for all patients. Children may be more sensitive than adults to the effects of ethanol (see **Special Warnings and Precautions for Use: Pediatric Use** section).

Injection Site Reactions
A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Hepatic Impairment
Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. Dose adjustment is recommended (see **Posology and Method of Administration: Hepatic Impairment** section)**.** Patients should be monitored closely for the development of profound myelosuppression (See **Clinical Pharmacology** section).

Pediatric Use
The safety and effectiveness of paclitaxel in pediatric patients has not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

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 Interactions with other medicinal products and other forms of interaction

Effects of Other Drugs on Paclitaxel

Cisplatin: In clinical combination trials, myelosuppression was more profound and paclitaxel clearance was reduced by approximately 20% when paclitaxel was given AFTER cisplatin as compared to when paclitaxel was given BEFORE cisplatin.

Substrates, Inducers, Inhibitors of Cytochrome P450 2C8 and 3A4: The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel concomitantly with known substrates, inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) or inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, montelukast, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*.

The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Cimetidine: The clearance of paclitaxel is not affected by cimetidine pretreatment.

Effects of Paclitaxel on Other Drugs
Doxorubicin: Sequence effects characterized by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered BEFORE doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and three-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Epirubicin: 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.

Other Interactions
There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients.

4.6 Pregnancy and Lactation
Pregnancy, lactation and fertility
Paclitaxel may cause fetal harm when administered to a pregnant woman. Paclitaxel has been shown to be embryotoxic and fetotoxic in rabbits and to decrease fertility in rats. There are no studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with paclitaxel. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard. It is not known whether paclitaxel is excreted in human milk. Breast-feeding should be discontinued for the duration of paclitaxel therapy.

Given the mutagenic potential of paclitaxel, an effective contraception is required for both male and female patients during treatment and up to 6 months after ending treatment. As paclitaxel may decrease male fertility, preservation of sperm may be considered for the purpose of later fatherhood.
4.7 Effects on Ability to Drive and to 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 pre-medications 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 severe hematologic 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, extravasation can 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).

Infections and infestations

Very common:	infection
Uncommon:	septic shock
Rare:*	pneumonia, sepsis

Blood and the lymphatic system disorders

Very common:	myelosuppression, neutropenia, anemia, thrombocytopenia, leukopenia, fever, bleeding
Rare:	febrile neutropenia
Very rare:*	acute myeloid leukemia, myelodysplastic syndrome

Immune system disorders

Very common:	minor hypersensitivity reactions (mainly flushing and rash)
Uncommon:	significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic edema, respiratory distress, generalised urticaria, edema, back pain, chills)
Rare:*	anaphylactic reactions (with fatal outcome)
*Very rare**:	anaphylactic shock

Metabolism and nutrition disorders

*Very rare**:	anorexia
*Not known**:	tumor 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:*	reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended photopsia, visual floaters
*Not known**:	macular oedema

Ear and labyrinth disorders

*Very rare**:	hearing loss, tinnitus, vertigo, ototoxicity

Cardiac disorders:

Very common:	abnormal ECG
Common:	bradycardia
Uncommon:	cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction
*Very rare**:	atrial fibrillation, supraventricular tachycardia

Vascular disorders

Very common:	hypotension
Uncommon:	hypertension, thrombosis, thrombophlebitis
*Very rare**:	shock

Respiratory, thoracic and mediastinal disorders

Rare:*	dyspnea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism
*Very rare**:	cough

Gastrointestinal disorders

Very common:	nausea, vomiting, diarrhea, mucosal inflammation
Rare:*	bowel obstruction, bowel perforation, ischemic colitis, pancreatitis

*Very rare**:	mesenteric thrombosis, pseudomembranous colitis, esophagitis, constipation, ascites

Hepatobiliary disorders

*Very rare**:	hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)

Skin and subcutaneous tissue disorders

Very common:	alopecia
Common:	transient and mild nail and skin changes
*Rare**:	pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, radiation recall
*Very rare**:	Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
*Not known**:	scleroderma, cutaneous lupus erythematosus

Musculoskeletal, connective tissue and bone disorders

Very common:	arthralgia, myalgia
*Not known**:	systemic lupus erythematosus

General disorders and administration site conditions

Common:	injection site reactions (including localized edema, pain, erythema, induration, on occasion extravasation can result in cellulitis)
*Rare**:	asthenia, malaise, pyrexia, dehydration, edema

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 post marketing 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 of treatments 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. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in paediatric patients may be associated with acute ethanol toxicity (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Pediatric Use** section).

5. CLINICAL PHARMACOLOGY
5.1 Pharmacodynamic properties
Mechanism of Action
Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers. It stabilizes microtubules by preventing depolymerization resulting in the inhibition of the normal dynamic reorganization of the microtubule network essential for cellular functions. Paclitaxel also 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, and infusion schedules, ranging from 3 to 24 hours and have been shown to be non-linear and saturable with a disproportionately large increase in C_{max} and AUC with increasing dose accompanied

by an apparent dose-related 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 non-significant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m^2), but no observed increase in plasma exposure. (See **Posology and Method of Administration: Hepatic Impairment** section and **Special Warnings and Precautions for Use: Hepatic Impairment** section.)

5.3 Preclinical safety data
Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of paclitaxel has not been studied. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay. Decreased fertility and decreased numbers of implantations and live fetuses occurred in rats receiving paclitaxel. Paclitaxel has also been shown to be embryotoxic and fetotoxic in rabbits receiving the drug during organogenesis. (See **Pregnancy and Lactation.**)

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

Vial before opening

Please refer to outer carton.

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 withdrawal.

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

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.

6.2 Special precautions for storage

Store below 25°C. Protect from light.

6.3 Nature and contents of container

30 mg in 5 mL glass vials: 1’s
100 mg in 16.7 mL glass vials: 1’s
150 mg in 25 mL glass vials: 1’s
300 mg in 50 mL glass vials: 1’s

Not all pack sizes may be marketed.

7. PRODUCT REGISTRANT

Novartis (Singapore) Pte Ltd
20 Pasir Panjang Road,
#10-25/28, Mapletree Business City,
Singapore 117439

8. DATE OF REVISION

Feb 2022