

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Paclitaxel Ebewe® 6 mg/mL concentrate for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of Paclitaxel Ebewe® concentrated injection contains 6 mg of paclitaxel.

Excipient with known effect: Ethanol.

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 PEG-35 castor oil and absolute ethanol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Injection, concentrated.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Primary treatment of ovarian cancer in combination with a platinum agent.

Treatment of metastatic ovarian cancer and metastatic breast cancer, after failure of standard therapy.

Treatment of non-small cell lung cancer (NSCLC).

Adjuvant treatment of node-positive breast cancer administered sequentially to doxorubicin and cyclophosphamide.

Treatment of metastatic cancer of the breast, in combination with trastuzumab (Herceptin), in patients who have tumours that overexpress HER-2 and who have not received previous chemotherapy for their metastatic disease.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Product is for single use in one patient only.

All patients must be premedicated before paclitaxel is administered to prevent severe hypersensitivity effects (see Section 4.4 Special warnings and precautions for use). Such premedication may consist of:

- dexamethasone 20 mg orally (or its equivalent), approximately 12 and 6 hours prior to starting the paclitaxel infusion.
- promethazine 25 mg or 50 mg intravenously or other suitable H1-antagonist, 30 minutes prior to starting the paclitaxel infusion
- cimetidine 300 mg or ranitidine 50 mg by intravenous infusion over 15 minutes, starting 30 minutes prior to the paclitaxel infusion.

Repeat courses of Paclitaxel Ebewe Injection Concentrate should not be administered to patients with solid tumors until the neutrophil count is at least 1.5×10^9 cells/L and the platelet count is at least 100×10^9 cells/L. Patients who experience severe neutropenia ($< 0.5 \times 10^9$ cells/L) or severe peripheral neuropathy should receive a dosage reduction by 20% for subsequent courses.

For primary treatment of ovarian cancer - it is recommended that paclitaxel be used at a dose of 135 mg/m^2 , administered intravenously over three hours, followed by cisplatin 75 mg/m^2 . The infusion should be repeated every three weeks.

For the treatment of metastatic ovarian cancer or metastatic breast cancer - it is recommended that paclitaxel be used as a single agent at a dose of 175 mg/m^2 . Paclitaxel should be administered as an intravenous infusion over three hours. The infusion should be repeated every three weeks as tolerated. Patients have tolerated treatment with up to nine cycles of paclitaxel therapy, but the optimal course of therapy remains to be established.

For primary or secondary treatment of NSCLC (non-small cell lung cancer) - the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over three hours with a three-week interval between courses.

For node-positive breast cancer - the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over three hours every three weeks for four courses following doxorubicin and cyclophosphamide combination therapy.

For overexpression of HER-2 breast cancer - paclitaxel 175 mg/m^2 administered intravenously over three hours with a three-week interval between courses for six cycles. Herceptin 2 mg/kg administered intravenously once a week until progression of disease after an initial loading dose of 4 mg/kg bodyweight.

Repetition of a course of paclitaxel is not recommended until the patient's neutrophil count is at least 1.5×10^9 cells/L ($1,500 \text{ cells/mm}^3$) and the platelet count is at least 100×10^9 cells/L ($100,000 \text{ cells/mm}^3$). If there is severe neutropenia (neutrophil count less than 0.5×10^9 cells/L for seven or more days), severe peripheral neuropathy or severe mucositis during paclitaxel therapy, the dose of paclitaxel in subsequent courses should be reduced by 20% (see Section 4.4 Special warnings and precautions for use). The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

Hepatic impairment

Inadequate data are available to recommend dosage alteration in patients with mild, moderate and severe hepatic impairments (see Section 4.4 Special warnings and precautions for use).

Paediatric population

Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy (see Section 4.4 Special warnings and precautions for use).

Method of administration

For intravenous use:

For instructions on reconstitution of the medicine before administration, see Section 6.6 Special precautions for disposal and other handling.

4.3. CONTRAINDICATIONS

Patients who have exhibited hypersensitivity reactions to paclitaxel, other taxanes or to any excipient especially patients who have a history of hypersensitivity effects to PEG-35 castor oil (Cremophor EL) or medicines formulated in PEG-35 castor oil (e.g. ciclosporin for injection concentrate, teniposide for injection concentrate).

Paclitaxel should not be administered to patients with solid tumours who have baseline neutrophils counts of $< 1.5 \times 10^9$ cells/L.

Paclitaxel is contraindicated during lactation (see Section 4.6 Fertility, pregnancy and lactation – Use in Pregnancy and Use in Lactation).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Paclitaxel should be administered under the supervision of medical staff experienced in the use of cancer chemotherapeutic agents. Since significant hypersensitivity effects may occur, appropriate supportive equipment should be available.

Paclitaxel should be given before a platinum compound when it is given in combination with a platinum compound, e.g. cisplatin (see Section 4.5 Interactions with other medications and other forms of interactions).

Premedication

In order to minimise the possibility of hypersensitivity effects due to histamine release, patients must be premedicated before every treatment cycle of paclitaxel. Premedication should include corticosteroids (e.g. dexamethasone), antihistamines (e.g. diphenhydramine or promethazine) and an H₂-receptor antagonist (e.g. cimetidine or ranitidine). (See Section 4.2 Dose and method of administration.) The characteristic symptoms of hypersensitivity effects are dyspnoea and hypotension (both requiring treatment), angioedema and widespread urticaria. In clinical trials, 2% of patients treated with paclitaxel experienced severe hypersensitivity. One of these effects was fatal in a patient treated without premedication.

Paclitaxel Ebewe Injection Concentrate must not be used in patients who have exhibited hypersensitivity effects to paclitaxel.

Haematologic Toxicity

Neutropenia (See Section 4.8 Undesirable effects).

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Blood counts should be frequently monitored during treatment with paclitaxel. Extreme care should be taken when paclitaxel is given to patients with a pretreatment neutrophil count of less than 1.5×10^9 cells/L ($1,500$ cells/mm³). Pretreatment with paclitaxel should not be administered until the patient's neutrophil count is greater than 1.5×10^9 cells/L ($1,500$ cells/mm³) and the platelet count is greater than 100×10^9 cells/L ($100,000$ cells/mm³).

If there is severe neutropenia during a course of paclitaxel (i.e. neutrophil count less than 0.5×10^9 cells/L (500 cells/mm³) for seven or more days), the dose of paclitaxel in subsequent cycles should be reduced by 20%. Previous radiation therapy may induce more severe myelosuppression. There is little information available from such patients at doses above 135 mg/m².

Cardiovascular toxicity

Hypotension, hypertension and bradycardia have been observed during Paclitaxel Ebewe Injection Concentrate administration, but generally do not require treatment. Frequent monitoring of vital signs, particularly during the first hour of Paclitaxel Ebewe Injection Concentrate infusion is recommended. (See also Section 4.8 Undesirable effects).

Electrocardiographic monitoring is recommended for patients with serious conduction abnormalities, and should be commenced for patients who develop abnormal cardiovascular symptoms or signs during monitoring of vital signs.

Severe cardiac conduction abnormalities have been reported rarely during paclitaxel therapy. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous electrocardiographic monitoring should be commenced and performed during subsequent therapy with paclitaxel. (See also Section 4.8 Undesirable effects). Severe cardiovascular events have been observed more frequently in patients with non-small cell lung cancer (NSCLC) than breast or ovarian cancer.

When paclitaxel is used in combination with trastuzumab or doxorubicin for treatment of metastatic breast cancer, monitoring of cardiac function is recommended. When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examinations, ECG, echocardiogram, and/or multi-gated radionuclide angiography (MUGA) scan. Cardiac function should be further monitored during treatment (e.g. every 3 months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m^2) 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).

Gastrointestinal toxicity

In patients receiving Paclitaxel who complain of abdominal pain with other signs and symptoms, bowel perforation should be excluded.

Injection Site Reaction

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.

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.

Anaphylaxis and Severe Hypersensitivity Reactions

Severe hypersensitivity (anaphylactoid) reactions characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred rarely in premedicated patients receiving paclitaxel.

Rare fatal reactions have occurred in patients despite pretreatment.

Cross-hypersensitivity between paclitaxel and other taxane products has been reported and may include severe reactions such as anaphylaxis. Patients with a previous history of hypersensitivity to other taxanes should be closely monitored during initiation of paclitaxel therapy.

Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. Patients receiving paclitaxel should be under continuous observation for at least the first 30 minutes following the start of the infusion and frequently thereafter. In case of a severe hypersensitivity reaction, paclitaxel infusion should be discontinued immediately and appropriate treatment given as indicated for anaphylaxis. The patient should not be rechallenged with the drug. Minor hypersensitivity reactions such as flushing, skin reactions, etc., do not require interruption of therapy (see also Section 4.8 Undesirable effects).

Hypotension and bradycardia

Patients may develop hypotension and bradycardia during paclitaxel treatment, but generally not to a level requiring treatment. Vital signs should be monitored frequently, particularly during the first hour of paclitaxel infusion. Only patients with serious conduction abnormalities require continuous cardiac monitoring (see Conduction abnormalities (above) and Section 4.8 Undesirable effects).

Nervous system

The occurrence of peripheral neuropathy is frequent and the development of severe symptoms is dose-dependent.

Patients with pre-existing neuropathy should be carefully monitored. Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% for all subsequent doses of paclitaxel is recommended (See Section 4.8 Undesirable effects).

In NSCLC patients, the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of neurotoxicity than usually seen in patients receiving single-agent paclitaxel.

Paclitaxel Ebewe Injection Concentrate contains absolute ethanol, 402 mg/mL and consideration should be given to possible central nervous system and other effects of absolute ethanol.

For instance, children may be more sensitive than adults to the effects of absolute ethanol.

Interstitial pneumonia

Paclitaxel in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of interstitial pneumonia.

Pseudomembranous colitis

Pseudomembranous colitis has been reported 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.

Mucositis

Severe mucositis has been reported which requires dose reduction (see Section 4.2 Dose and method of administration).

Ophthalmology

There have been reports of reduced visual acuity due to cystoid macular oedema (CMO) during treatment with paclitaxel as well as with other taxanes (see Section 4.8 Undesirable effects). Patients with visual impairment during paclitaxel treatment should seek a prompt and complete ophthalmologic examination. Paclitaxel should be discontinued if a CMO diagnosis is confirmed.

Use in hepatic impairment

There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering paclitaxel to patients with moderate impairment and dose adjustments should be considered. Patients with severe hepatic impairment must not be treated with paclitaxel.

Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3-4 myelosuppression. When paclitaxel is given as a 24-hour infusion to patients with moderate to severe hepatic impairment, increased myelosuppression may be seen as compared to patients with mildly elevated liver function tests given 24-hour infusions. Patients should be monitored closely for the development of profound myelosuppression (see Section 4.2 Dose and method of administration). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see Section 5 Pharmacological properties).

No data are available for patients with severe baseline cholestasis.

Use in the elderly

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 randomised 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 medical survival than younger patients, but no other efficacy parameters favoured the younger group.

Paediatric use

The safety and effectiveness of paclitaxel in children have not been established. There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in paediatric patients in which paclitaxel was infused over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of 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.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cisplatin

The recommended regimen of paclitaxel administration for the first-line chemotherapy of ovarian carcinoma is for paclitaxel to be given before cisplatin. In a dose-finding trial in which paclitaxel was administered as a 24-hour infusion and cisplatin was administered as a 1 mg/min infusion, myelosuppression was more profound when paclitaxel was given after cisplatin than when paclitaxel was given before cisplatin. Pharmacokinetic data demonstrated a reduction in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

Ketoconazole

As ketoconazole may inhibit the metabolism of paclitaxel, patients receiving paclitaxel and ketoconazole should be closely monitored or the combination of these medicines should be avoided.

Doxorubicin

Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination and are given closer in time. Paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see Section 4.2 Dose and method of administration). However, data from a trial using bolus doxorubicin and three-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Cimetidine

Paclitaxel clearance is not affected by cimetidine premedication.

Medicines metabolised in the liver

The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Clinical studies have demonstrated that CYP2C8 mediated metabolism of paclitaxel, to 6 α -hydroxypaclitaxel, is the major metabolic pathway in humans. Concurrent administration to 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 CYP2C8 and 3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil, deferasirox, trimethoprim) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine, St. John's wort) either CYP2C8 or 3A4.

In the clinical trial of paclitaxel in combination with trastuzumab (Herceptin), mean serum trough concentration of trastuzumab were consistently elevated 1.5-fold as compared with

serum concentrations of trastuzumab in combination with anthracycline plus cyclophosphamide (AC).

Arthralgia or myalgia adverse events of paclitaxel appear to be of a higher incidence in patients being treated concurrently with filgrastim (granulocyte colony stimulating factor (G-CSF)).

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Following treatment with intravenous paclitaxel at a dose of 1 mg/kg (6 mg/m²), rats showed decreased fertility and toxicity in unborn offspring. Paclitaxel administered intravenously to rabbits during organogenesis at a dose of 3 mg/kg (33 mg/m²) was toxic to both mother and foetus.

Infertility in Females and Males

Based on findings in animal studies, paclitaxel may impair fertility in females and males of reproductive potential.

Use in pregnancy

Category D

Paclitaxel Ebewe Injection Concentrate may cause foetal harm when administered to a pregnant woman. There is no adequate data from the use of paclitaxel in pregnant women. Studies have shown paclitaxel to be embryotoxic and foetotoxic in rabbits at an intravenous dose of 3 mg/kg (33 mg/m²) given during organogenesis. Paclitaxel is toxic to rat foetuses at a dose of 1 mg/kg (6 mg/m²).

As with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women. Therefore, paclitaxel should not be used during pregnancy unless clearly necessary. Examination revealed that no gross external, soft tissue or skeletal alterations occurred. There are no studies in pregnant women. Women of children-bearing potential should be advised to avoid becoming pregnant and to inform the treating physician immediately should this occur during therapy with Paclitaxel Ebewe Injection Concentrate. If Paclitaxel Ebewe Injection Concentrate is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard.

Females and Males of Reproductive Potential

Female and male patients of fertile age, and/or their partners should use contraceptions for at least 6 months after treatment with paclitaxel.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Use in lactation

Paclitaxel is contraindicated during lactation (see Section 4.3 Contraindications). It is not known whether paclitaxel is excreted in human milk. The evidence from many medicines would suggest that paclitaxel could be excreted in breast milk, though this has not been established. Because of the potential for serious adverse effects in breastfeeding infants, it is recommended that breastfeeding be discontinued when receiving paclitaxel therapy.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

It is not known whether paclitaxel interferes with the ability to drive and use machines; however, Paclitaxel Ebewe does contain alcohol. Paclitaxel is likely to produce minor or moderate adverse effects, which may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines. Patients should refrain from driving or using machines until they know that paclitaxel does not negatively affect these abilities.

4.8. UNDESIRABLE EFFECTS

Unless otherwise noted, the following is based on the experience of 812 patients treated in phase II and III clinical trials.

The frequency and severity of adverse effects are generally similar between patients receiving paclitaxel for the treatment of ovarian, breast or lung cancer. None of the observed effects were clearly influenced by age.

Unless stated otherwise percent figures, where given, are based on observed incidence when using the recommended dosing regimen. If other regimens are used, the incidence of effect may be higher.

Safety of the paclitaxel/ platinum combination has been investigated in a large randomised trial in ovarian cancer and in two-phase III trials in NSCLC (non-small cell lung cancer). Unless otherwise mentioned the combination of paclitaxel with platinum agents did not result in any clinically relevant changes to the safety profile of single-agent paclitaxel.

Adverse effects reported were those occurring during or following the first course of therapy, and have, where possible, been grouped by frequency according to the following criteria:

Very common: $\geq 1/10$; common: $\geq 1/100$ and $< 1/10$; uncommon: $\geq 1/1,000$ and $< 1/100$; rare: $\geq 1/10,000$ and $< 1/1,000$ and 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: sepsis, peritonitis, pneumonia

Cardiovascular

Very common: hypotension
Common: bradycardia, ECG abnormalities (nonspecific repolarisation and sinus tachycardia).
Uncommon: ECG abnormalities (premature beats), cardiomyopathy
Rare: myocardial infarction, congestive heart failure (typically in patients who have received other chemotherapy, notably anthracyclines)
Very rare: atrial fibrillation, supraventricular tachycardia

Six severe cardiovascular events possibly related to paclitaxel administration occurred including asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrioventricular block (two patients), and syncopal episodes (two patients, in one associated with severe hypotension and coronary stenosis resulting in death). Severe hypotensive effects have been associated with serious hypersensitivity effects and have required intervention.

Haematological

- Very common:*** myelosuppression, thrombocytopenia, leucopenia, fever, bleeding, anaemia, neutropenia (overall, 52% of the patients experienced severe grade IV neutropenia and 56% had grade III/IV severe neutropenia on their first course. Neutrophil nadirs occurred at a median of eleven days after paclitaxel administration)
- Common:*** febrile neutropenia (associated with an infectious episode, including urinary tract infection (UTI) and upper respiratory tract infection (URTI))
- Rare:*** five septic episodes, which were associated with severe neutropenia attributable to paclitaxel administration, had a fatal outcome
- Very Rare:*** acute myeloid leukaemia, myelodysplastic syndrome
- Patients who have received prior radiation or cisplatin therapy exhibit more frequent myelosuppression, which is generally of greater severity (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Reports of thrombocytopenia after paclitaxel therapy are less frequent and less severe than neutropenia, with platelet nadir ($< 50 \times 10^9$ cells/L) observed eight or nine days after paclitaxel administration in 5% of patients. Haemorrhage has been reported in patients receiving paclitaxel but this does not appear to be related to thrombocytopenia. Patients (3%) may require platelet transfusions.

Not known: Disseminated intravascular coagulation.

Hepatobiliary

- Very common:*** elevated alkaline phosphatase; elevated AST; elevated ALT
- Common:*** elevated bilirubin
- Rare:*** hepatic necrosis (leading to death), hepatic encephalopathy (leading to death)

Immune System Disorders

- Very common:*** minor hypersensitivity reactions (mainly flushing and rash)
- Common:*** dyspnoea, hypotension, chest pains, tachycardia
- Uncommon:*** significant hypersensitivity reactions requiring therapy (e.g. hypotension, angioneurotic oedema, bronchospasm, respiratory distress, generalised urticaria, oedema, back pains, pain in extremities, chills, diaphoresis). The most frequent symptoms observed during severe reactions were dyspnoea, flushing, chest pain and tachycardia. Abdominal pain, pain in the extremities, hyperhidrosis, and hypertension were also noted.
- Infections: Febrile neutropenia occurred in 5% of all courses and 30% of all courses were associated with an infectious episode. The most common infections involve the upper respiratory tract, urinary tract and blood (sepsis). In phase II clinical trials, five septic episodes resulted in death.
- Rare:*** anaphylactic reactions
- Very Rare:*** anaphylactic shock

Vascular Disorders

<i>Very common:</i>	hypotension
<i>Uncommon:</i>	hypertension, thrombosis, thrombophlebitis
<i>Very Rare:</i>	shock
<i>Not known:</i>	phlebitis

Metabolism and nutrition disorders

<i>Very Rare:</i>	anorexia
<i>Not Known:</i>	tumor lysis syndrome

Gastrointestinal

<i>Very common:</i>	nausea, vomiting, diarrhoea, mucositis (these manifestations were usually mild to moderate at the recommended dose)
<i>Rare:</i>	bowel obstruction, ischaemic colitis, pancreatitis, bowel perforation (there have been several cases of bowel perforation associated with patients receiving paclitaxel. Patients receiving paclitaxel who complain of abdominal pain with other signs and symptoms should have bowel perforation excluded) Neutropenic enterocolitis has been reported
<i>Very rare:</i>	mesenteric thrombosis, pseudomembranous colitis, neutropenic colitis, ascites, oesophagitis, constipation

Musculoskeletal, Connective Tissue and Bone Disorders

<i>Very common:</i>	arthralgia; myalgia (the symptoms were usually transient occurring two to three days after paclitaxel administration and resolving within a few days)
<i>Not Known:</i>	systemic lupus erythematosus

Psychiatric disorders

<i>Very rare:</i>	confusional state
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Neurological

<i>Very common:</i>	neurotoxicity (mainly: peripheral neuropathy. Peripheral neuropathy occurs and is dose-dependent with 60% of patients experiencing grade I toxicity, 10% grade II and 2% grade III at the recommended doses. Neuropathy was present in 87% of patients at higher doses. Severity of symptoms also increased with dose; 4% of patients experienced severe symptoms at the recommended dose versus 10% at higher doses. Neurological symptoms may occur following the first course and symptoms may worsen with increasing exposure to paclitaxel. Peripheral neuropathy was the cause of paclitaxel discontinuation in 2% of patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation).
<i>Rare:</i>	motor neuropathy (with resultant minor distal weakness). Optic nerve and/or visual disturbances (scintillating scotomata) particularly in patients who have received higher doses than recommended; these effects generally have been reversible; motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension.

There is a report of a grand mal seizure in a patient receiving paclitaxel and the seizure recurred after treatment with paclitaxel was recommenced. There is also a second report of a grand mal seizure in a patient with significant hepatic impairment during infusion with paclitaxel.

Very rare: grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache

Eye disorders

Very rare: Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended.

Ear and labyrinth disorders

Very rare: hearing loss, ototoxicity, tinnitus, vertigo

Respiratory, thoracic and mediastinal disorders

Rare: respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion

Very Rare: cough

Skin and appendages

Very common: alopecia

Common: transient and mild nail and skin changes

Rare: pruritus, rash, erythema, radiation recall dermatitis, recall dermatitis. Local effects: phlebitis following intravenous administration has been reported. Extravasation leading to oedema, pain, erythema and induration has been reported. On occasions, extravasation can lead to cellulitis. Skin discolouration may also occur.

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

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.

General Disorders and Administration Site Conditions

Common: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis).

Rare: pyrexia, dehydration, asthenia, oedema, malaise

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discolouration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. 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.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of paclitaxel

safety. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

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.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Investigations

Common: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase

Uncommon: severe elevation in bilirubin

Rare: increase in blood creatinine

Combination treatment

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, diarrhoea, 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.

Postmarketing Experience

The following additional adverse effects have been identified during post-approval use of Paclitaxel Ebewe Injection Concentrate. Because their reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to medicine exposure.

Infections and infestations: pneumonia, sepsis

Cardiac Disorders: atrial fibrillation, supraventricular tachycardia, reduction of left ventricular ejection fraction, ventricular failure

Hematological Disorders: acute myeloid leukaemia, myelodysplastic syndrome

Immune System Disorders: anaphylactic reactions (with fatal outcome); anaphylactic shock, cross-hypersensitivity between paclitaxel and other taxanes has been reported

Metabolic, and Nutrition

Disorders: anorexia, tumour lysis syndrome

Psychiatric Disorder: confusional state

Vascular Disorders: shock

Respiratory, Thoracic and

Mediastinal Disorders: dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough

Gastrointestinal Disorders: bowel obstruction, bowel perforation, ischemic colitis, pancreatitis, mesenteric thrombosis, pseudoemembranous colitis, oesophagitis, constipation, ascites

Neurological Disorders: autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia, paresthesia, hyperesthesia.

Eye Disorders: photopsia, visual floaters, cystoid macular oedema, macular oedema.

Ear and Labyrinth Disorders: hearing loss, tinnitus, vertigo, ototoxicity

Skin and Subcutaneous

Tissue Disorders: Stevens- Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet), scleroderma, pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, cutaneous lupus erythematosus.

Musculoskeletal, Connective

Tissue and Bone Disorders: systemic lupus erythematosus, scleroderma.

Investigations: increase in blood creatine.

General Disorders and

Administration Site Conditions: asthenia, malaise, pyrexia, dehydration, oedema.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. OVERDOSE

There is no known antidote for paclitaxel overdose.

At present, there is no specific treatment for paclitaxel overdosage. In case of overdose, the patient should be closely monitored. Probable consequences of an overdosage are mucositis, severe bone marrow suppression and peripheral neurotoxicity and treatment should be supportive.

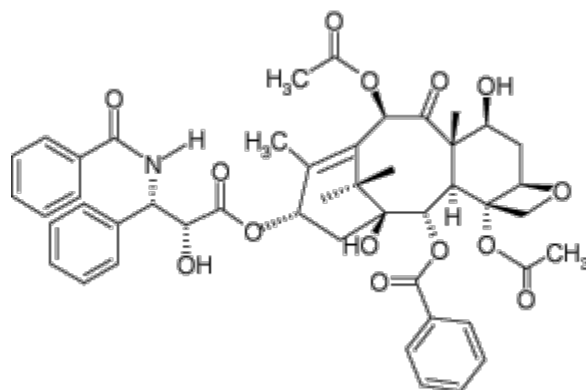
Overdosage in paediatric patients may be associated with acute ethanol toxicity. Treatment is symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Paclitaxel is a natural product with antitumour activity. Its Molecular formula: $C_{47}H_{51}NO_{14}$ (Molecular weight: 853.9), CAS: 33069-62-4 and its chemical structure is:



Mechanism of action

Paclitaxel is an antimicrotubule antineoplastic agent. It promotes microtubule assembly by enhancing the polymerisation of tubulin, the protein subunit of spindle microtubules, even in the absence of the mediators normally required for microtubule assembly (e.g. guanosine triphosphate (GTP)), thereby inducing the formation of stable, non-functional microtubules. While the precise mechanism of action of the medicine is not completely known, paclitaxel disrupts the dynamic equilibrium within the microtubule system and blocks cells in the late G2 phase and M phase of the cell cycle, inhibiting cell replication and impairing function of nervous tissue.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

After paclitaxel is administered intravenously, its plasma concentration declines biphasically.

Distribution

The first phase shows rapid decline, representing distribution of paclitaxel to the peripheral compartment and elimination. This initial phase is followed by a relatively slow elimination of paclitaxel from the peripheral compartment.

The following ranges for the pharmacokinetic parameters have been determined in patients given doses of 135 and 175 mg/m^2 as 3- and 24-hour infusions of paclitaxel. Mean terminal half-life: 3.0 to 52.7 hours; total body clearance: 11.6 to 24.0 $L/hour/m^2$; mean steady-state volume of distribution: 198 to 688 L/m^2 . These indicate extensive distribution of paclitaxel outside the vascular system and/or tissue binding. The volume of distribution is reduced in female subjects. The following mean values for the pharmacokinetic parameters have been reported following a three-hour infusion of 175 mg/m^2 paclitaxel. Mean terminal half-life: 9.9 hours, mean total body clearance: 12.4 $L/hour/m^2$. The serum protein binding of paclitaxel is 89%. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine does not affect protein binding of paclitaxel.

Metabolism

The liver is thought to be the primary site of metabolism for paclitaxel.

Excretion

The mean cumulative urinary recovery of unchanged paclitaxel has been reported to be 1.8 to 12.6% of the dose, indicating extensive non-renal clearance.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

In vitro studies (chromosome abnormalities in human lymphocytes) and *in vivo* (micronucleus test using mice) mammalian test systems have shown paclitaxel to be mutagenic. When tested using the Ames test or the CHO/HGPRT (Chinese hamster ovary/ hypoxanthine-guanine phosphoribosyl transferase) gene mutation assay, paclitaxel did not induce mutagenicity.

Carcinogenicity

No studies have examined the carcinogenic potential of paclitaxel; however, medicines similar to paclitaxel are carcinogens.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Each mL contains absolute ethanol 402 mg, PEG-35 castor oil 522 mg.

6.2. INCOMPATIBILITIES

Avoid contact of paclitaxel solutions with plasticised polyvinyl chloride (PVC) equipment, infusion lines or devices used when preparing infusion solutions. Prepare and store diluted paclitaxel solutions in glass or polyethylene containers. These precautions are to avoid leaching of the plasticiser DEHP (di-[2-ethylhexyl] phthalate) from PVC infusion bags or sets. Paclitaxel solutions should be administered through polyethylene lined administration sets (e.g. Gemini 20 giving set) using an IMED pump.

This medicine must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3. SHELF LIFE

3 years from date of manufacture.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2° - 8°C for not more than 24 hours after preparation.

A shelf life of 14 days at 2° to 8°C (refrigerate; do not freeze) for facilities preparing paclitaxel solutions reconstituted under controlled aseptic conditions for IV infusion.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5. NATURE AND CONTENTS OF CONTAINER

30 mg in 5 mL glass vials: 1's and 5'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

600 mg in 100 mL glass vials: 1's

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation for intravenous administration

Avoid contact of paclitaxel solutions with plasticised polyvinyl chloride (PVC) equipment, infusion lines or devices used when preparing infusion solutions. Prepare and store diluted paclitaxel solutions in glass or polyethylene containers. These precautions are to avoid leaching of the plasticiser DEHP (di-[2-ethylhexyl] phthalate) from PVC infusion bags or sets. Paclitaxel solutions should be administered through polyethylene lined administration sets (e.g. Gemini 20 giving set) using an IMED pump.

Paclitaxel Ebewe Injection Concentrate must be diluted prior to intravenous infusion. It should be diluted in glucose 5% or sodium chloride 0.9% intravenous infusion. Dilution should be made to a final concentration of 0.3 to 1.2 mg/mL.

After the final dilution of Paclitaxel Ebewe Injection Concentrate, the bottle should be swirled gently to disperse the paclitaxel. Do not shake.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2° - 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 of cytotoxic medicines (see Handling and disposal, below).

Facilities preparing paclitaxel solutions reconstituted under controlled aseptic conditions for IV infusion, may apply a shelf life of 14 days at 2° to 8°C (refrigerate; do not freeze) when diluted with glucose 5% or sodium chloride 0.9% for intravenous infusion and stored in glass or polyethylene containers. Diluted solutions prepared this way have been shown to be chemically stable for these periods. Administration should be completed within 24 hours of the start of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic medicines.

Filtration. A microporous membrane of 0.22 microns or less in size should be used as the in-line filter for all infusions of paclitaxel. The IMED 0.2 micron add-on filter set composed of polysulfone and the IVEX II 0.2 micron filter composed of cellulose have both been found to be suitable for Paclitaxel Injection Concentrate.

Devices with spikes should not be used with vials of Paclitaxel Ebewe Injection Concentrate since they can cause the stopper to collapse, resulting in a loss of sterile integrity of the Paclitaxel Ebewe Injection Concentrate solution.

Preparation and administration precautions

Paclitaxel is a cytotoxic anti-cancer medicine and, as with other potentially toxic compounds, caution should be exercised in handling Paclitaxel. The use of gloves is recommended. Following topical exposure, tingling, burning and redness have been observed. 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. 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 medicine administration.

Handling and disposal

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

Care must be taken whenever handling cytotoxic products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Novartis New Zealand Ltd
PO Box 99102
Newmarket
Auckland 1149
Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

14/10/2016

10. DATE OF REVISION OF THE TEXT

16/04/2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes
4.2	Additional information in dosage adjustment: <ul style="list-style-type: none"> - Addition of severe mucositis as symptom requiring dosage adjustment - Addition of information concerning hepatic impairment - Addition of information concerning paediatric population
4.3	Addition of hypersensitivity to other taxanes as a contraindication
4.4	Additional information under Cardiovascular Toxicity Additional information under Anaphylaxis and Severe Hypersensitivity reactions Addition of precautions “Interstitial pneumonia”, “Pseudomembranous colitis”, “Mucositis” and “Ophthalmology”
4.5	Additional information under subheadings “Cisplatin”, “Doxorubicin” and “Medicines metabolised by the liver”

Section Changed	Summary of new information
4.7	Additional information regarding the effects of paclitaxel on driving.
4.8	Addition of “bronchospasm, pain in extremities, diaphoresis” under Immune system disorders Addition of “cystoid macular oedema” under Eye disorders Addition of “scleroderma” under Musculoskeletal, connective tissue and bone disorders
4.9	Additional information regarding monitoring and treatment in cases of overdose