1. **NAME OF THE MEDICINAL PRODUCT**

Ebetaxel®

(Paclitaxel "Ebewe")

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Vials containing 30mg, 100mg, 150mg, 210mg or 300mg paclitaxel as a 6mg/mL solution.

3. **PHARMACEUTICAL FORM**
Concentrate for solution for infusion.
Clear, colourless or weakly yellow coloured solution.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Ovarian cancer: First-line treatment of carcinoma of the ovary, in combination with cisplatin, including patients with advanced disease or residual disease (>1 cm) after initial laparotomy.
Second-line treatment of metastatic carcinoma of the ovary after failure of standard platinum containing therapy.

Breast cancer: Treatment of metastatic carcinoma of the breast in patients who have failed, or are not candidates for, standard anthracycline containing therapy.

Non-small cell lung cancer: Treatment of non-small cell lung cancer (NSCLC) in combination with cisplatin in patients who are not candidates for potentially curative surgery and/or radiation therapy.
Kaposi's sarcoma in patients with AIDS.

4.2 Posology and method of administration
Adults and elderly:
First-line treatment of ovarian cancer:
The recommended combination regimen for first-line treatment consists of paclitaxel 135mg/m^2 administered over 24 hours, followed by cisplatin 75mg/m^2, with a 3 week interval between courses (see Interaction with other medicinal products and other forms of interaction). Other combination regimens are being investigated.
Second-line treatment of ovarian and breast cancer:
The recommended dose of paclitaxel is 175mg/m^2 administered over a period of 3 hours, with a 3 week interval between courses.
Treatment of advanced NSCLC:
The recommended dose of paclitaxel is 175mg/m^2 administered over a period of 3 hours, followed by cisplatin 80mg/m^2, with a 3 week interval between courses.
Treatment of Kaposi's sarcoma:
The recommended dose is 135mg/m^2 administered over a period of 3 hours, with a 3 week interval between courses.
Special circumstances:
Patients with liver failure:
There are no clinical trials in patients with insufficient hepatic function. Available data are not adequate to make a dose recommendation for these patients (see Pharmacokinetic properties). Patients with severe liver failure should not receive paclitaxel.
Patients with kidney failure:
There are no clinical trials in patients with insufficient renal function. Available data are not adequate to make a dose recommendation for these patients (see Pharmacokinetic properties).
Use in children:
There are no clinical trials about efficacy and undesirable effects in paediatric patients (under 18 years of age). Therefore, paclitaxel currently is not recommended for use in children.
Use in elderly patients:
There are no clinical trials about efficacy and undesirable effects in geriatric patients (over 65 years of age). Therefore, paclitaxel currently is not recommended for use in elderly patients.
Subsequent doses of paclitaxel should be administered according to individual patient tolerance.
Paclitaxel should not be readministered until the neutrophil count is ≥1.5 x 10^9/L and the platelet count is ≥100 x 10^9/L. Patients who experience severe neutropenia (neutrophil count <0.5 x 10^9/L for ≥7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent cycles (see Special warnings and special precautions for use).
All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel, e.g.

Drug	Dose	Administration prior to paclitaxel
Dexamethasone	20mg oral	Approximately 12 and 6 hours
Diphenhydramine or chlorpheniramine	50mg IV 10mg IV	30 to 60 minutes
Cimetidine or ranitidine	300mg IV 50mg IV	30 to 60 minutes

Paclitaxel should be administered through an in-line filter with a microporous membrane ≤0.22 µm (see *Instructions for use/handling*).
Children: The dose of paclitaxel has not been established in children.

4.3 Contraindications
Paclitaxel is contra-indicated in patients who have a history of severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyoxyl castor oil.
Paclitaxel should not be used in patients with baseline neutrophils <1500/mm^3.

4.4 Special warnings and special precautions for use
Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.
Paclitaxel administration must take place in a hospital or an infirmary.
Intra-arterial administration of paclitaxel must be avoided.
Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. During the paclitaxel administration, the patient should be monitored. Regular monitoring of cardiovascular and respiratory vital signs is especially important during the first hour.
Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists before receiving paclitaxel. Paclitaxel should be given before cisplatin when used in combination.

Significant hypersensitivity reactions, characterised by dyspnoea, hypotension that requires treatment, angioedema and generalised urticaria have occurred in less than 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated. In case of severe hypersensitivity reactions paclitaxel infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with the drug.

Slight hypersensitivity reactions, e.g. skin reactions, flush, minor dyspnoea, insignificant hypotension, or tachycardia, do not require discontinuation of paclitaxel.

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be retreated until neutrophils recover to a level ≥1.5 x 10^9/L and platelets recover to a level ≥100 x 10^9/L.

Patients receiving paclitaxel are at increased risk of infection and/or bleeding because of neutropenia and thrombocytopenia; therefore, dental care should be carried out only if absolutely necessary during paclitaxel-containing therapy. Patients must be alerted to the importance of good dental hygiene.

Severe cardiac conduction abnormalities have been reported rarely. If patients develop significant conduction abnormalities during paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.
Severe cardiovascular events were observed more frequently in patients with NSCLC than in those with breast or ovarian carcinoma.
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.
Although the occurrence of *peripheral neuropathy* is frequent, the development of severe symptoms is unusual. If a patient should develop severe peripheral neuropathy, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel. In NSCLC patients, the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of severe neurotoxicity than single agent paclitaxel.
Patients who had received *prior therapy with neurotoxic agents* may experience dose-limiting cumulative neurotoxicity.
Paclitaxel is not recommended in patients with *moderately severe and severely impaired hepatic function*; a possible bone marrow depression due to paclitaxel could be amplified in these patients.
Relative contra-indications for the administration of paclitaxel are impaired hepatic function, Herpes zoster infection, Varicella zoster infection, severe infections, bone marrow depression, patients with prior chemotherapy or irradiation, and patients with a history of cardiac rhythm disturbances or myocardial infarction.
In patients with NSCLC, combination therapy with cisplatin plus paclitaxel more commonly leads to neurological undesirable effects than single agent paclitaxel.
Since Ebetaxel®/Paclitaxel "Ebewe" contains ethanol (401.66mg/mL), consideration should be given to possible CNS and other effects. This is especially true in alcoholics, patients with liver failure, and in patients with seizures or cerebral damage. Diphenhydramine premedication can intensify the effects of alcohol.

4.5 Interaction with other medicinal products and other forms of interaction
Concurrent or sequential therapy with other cytotoxic drugs or irradiation can intensify bone marrow depression due to paclitaxel.
During the administration of the recommended chemotherapy regimen for the first-line treatment of ovarian cancer, paclitaxel is 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 is given after cisplatin, patients show a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance.
Premedication with cimetidine does not influence the clearance of paclitaxel, although a cimetidine-related inhibition of cytochrome P450 has been observed in the liver; this inhibition does not seem to influence the efficacy of paclitaxel.
The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see *Pharmacokinetic properties*). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6alpha-hydroxypaclitaxel, is the major metabolic pathway in humans. Based on the current knowledge, clinically relevant interactions between paclitaxel and other substrates or inhibitors of CYP2C8 are not anticipated. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal drugs may be administered together without dosage adjustment. Further data on the potential of drug interactions between paclitaxel and other substrates or inhibitors of CYP3A4 are limited. Therefore, caution should be exercised when administering paclitaxel concurrently with known substrates or inhibitors of CYP3A4.
As a consequence of myelosuppression, a modified immune response is possible. Therefore, live vaccines should not be used in patients receiving therapy with paclitaxel. Similarly, they should avoid contact to persons who recently have been inoculated with oral live polio vaccine.

4.6 Pregnancy and lactation
There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm when administered to pregnant women.
Paclitaxel is contra-indicated during pregnancy and lactation.
Women should be advised to avoid becoming pregnant during therapy with paclitaxel and to inform the treating physician immediately should this occur.
It is not known whether paclitaxel is excreted in human milk.
Paclitaxel is contra-indicated during lactation. Breast feeing should be discontinued for the duration of paclitaxel therapy.
Paclitaxel has been shown to be both embryotoxic and fetotoxic in rabbits and to decrease fertility in rats.

4.7 Effects on ability to drive and use machines
Ebetaxel®/Paclitaxel "Ebewe" contains alcohol (*see List of excipients*); thus, paclitaxel administration may interfere with the ability to drive and use machines.

4.8 Undesirable effects
Results of clinical trials show that paclitaxel is generally tolerated well, if recommended doses and regimens are adhered to.
The frequency and severity of adverse events are dependent on the dose and general health (performance status) of the patient at the time of diagnosis, but are generally similar between patients receiving paclitaxel for the treatment of ovarian cancer, breast cancer or NSCLC. There is no correlation between the age of the patients and the severity of adverse events.
The following safety data relate to patients with ovarian or breast cancer treated with 175mg/m^2 single agent paclitaxel over a 3-hour infusion in phase III clinical trials.
Safety of the paclitaxel/platinum combination has been evaluated in a large randomised controlled clinical trial in ovarian cancer (24 hour infusion, GOG-111) and in major phase III trials in NSCLC (3 hour infusion). Unless otherwise specified, the combination of paclitaxel with platinum agents, or the infusion of paclitaxel over 24 hours, did not result in any clinically relevant changes to the safety profile of single agent paclitaxel.
The following adverse events were described:
Infections and infestations:
Very common:
Twenty-four percent of patients had an infectious episode. In the phase III clinical trials, 2 fatal infections were seen at the recommended dose and infusion schedule.
The most frequent infections related to neutropenia were genitourinary tract infections, respiratory tract infections, and sepsis.
Blood and the lymphatic system disorders:
Very common:
Haematopoiesis: The most frequent significant undesirable effect of paclitaxel is bone marrow suppression. Severe neutropenia (<0.5 x 10^9/L) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for 7 days or more. In general, neutropenia was quickly reversible.
Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir <50 x 10^9/L at least once while on study.
Anaemia was observed in 64% of patients, but was severe (Hb<5 mmol/L) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.
Myelosuppression was less frequent and less severe with a 3 hour infusion than with a 24 hour infusion schedule. The recommended paclitaxel/cisplatin regimen for the first-line treatment of ovarian cancer caused more severe myelosuppression than single dose paclitaxel using the recommended dose of 175mg/m^2 infused over 3 hours. However, there was no increase in clinical sequelae.
Very rare:
One case each of acute myeloid leukaemia and myelodysplastic syndrome have been reported.
Immune system disorders:

Very common:
Thirty-four percent of patients experienced minor reactions (in 17% of all courses), mainly flushing and rash; these did not require therapeutic intervention, nor did minor reactions prevent continuation of paclitaxel therapy.
Common:
After appropriate premedication, a significant hypersensitivity reaction (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in 2 patients (<1%).-
Nervous system disorders:
Very common:
Two-thirds of the patients had mild peripheral neuropathy, mainly manifested by paraesthesia.
Common:
Five percent of patients had severe peripheral neuropathy.
In NSCLC patients, the incidence of severe peripheral neuropathy is slightly greater (6%). Peripheral neuropathy can occur more frequently with increasing exposure to further cycles of chemotherapy with paclitaxel, and may necessitate the discontinuation of paclitaxel. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy; however, already present neuropathy symptoms may be amplified because of a cumulative toxic effect. Sensory neuropathy symptoms have usually improved or resolved within several months of paclitaxel discontinuation.
Very rare:
Grand mal seizures, encephalopathy, motor neuropathy with resultant minor distal weakness, autonomic neuropathy resulting in paralytic ileus, and orthostatic hypotension have been reported.
Eye disorders:
Very rare:
Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than recommended. Generally, these effects have been reversible.
Cardiac disorders:
Very common:
Hypotension and bradycardia were experienced by 22% and 5% of patients, respectively. The degree of change was usually mild and did not require therapeutic intervention.
Uncommon:
Abnormal ECGs were seen. In most cases, no clear relationship between paclitaxel and ECG alterations could be defined, and these alterations were of little or no clinical relevance.
Very rare:
Hypertension during paclitaxel therapy was described in very rare cases. Hypotension associated with septic shock and severe thrombotic events (upper extremity thrombosis and thrombophlebitis) were seen.
During paclitaxel therapy, the following cardiac events can occur: junctional ventricular tachycardia, tachycardia with bigeminy, AV block, syncope, cardiomyopathy, congestive heart failure, myocardial infarction and hypotension. These occur more frequently in patients who have received other chemotherapeutic drugs, notably anthracyclines, or in patients with NSCLC (see Special warnings and special precautions for use).
Gastrointestinal disorders:
Very common:
Gastrointestinal adverse events were usually mild to moderate: nausea/vomiting, diarrhoea and mucositis were reported in approximately 40%, 30% and 20% of patients, respectively.
Rare:
Bowel obstruction/perforation, and mesenteric thrombosis, including ischaemic colitis, have been described.
Neutropenic enterocolitis and pneumonia during concurrent irradiation have been described.
Hepato-biliary disorders:
Common:
Severe elevations (>5 x normal values) in AST (SGOT) and alkaline phosphatase were seen in 5% and 4% of patients, respectively.
Uncommon:
Severe elevations (>5 x normal values) of bilirubin was seen in 1% of patients.
Very rare:
Hepatic necrosis, hepatic encephalopathy and peripheral oedema have been reported.
Skin and subcutaneous tissue disorders:
Very common:
Alopecia was observed in almost all patients.
Very rare:
Exfoliative dermatitis has been described.
Steven-Johnson syndrome, epidermal necrolysis and erythema multiforme have been reported. It is not known if accompanying circumstances have contributed to the occurrence of these adverse events.
Musculoskeletal, connective tissue and bone disorders:
Very common:
Arthralgia or myalgia affected 60% of patients. Pain developed usually within 2 to 3 days after treatment and disappeared within 5 days.
General and administration site conditions:
Very common:
Injection site reactions may lead to localised oedema, pain, erythema, and induration in 13% of patients.
Rare:
Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e. "recall" phenomenon, has been reported in rare cases.
Cellulitis and depigmentation after extravasation have been reported.
Injury and poisoning:
Very rare:
Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

4.9 Overdose
There is no known antidote for paclitaxel overdose. The first possible complications of an overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group ATC code: cytostatic agent, L01C D01
Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. 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
Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations.
The pharmacokinetics of paclitaxel were determined following 3-hour and 24-hour infusions at doses of 135 and 175mg/m^2. Mean terminal half-life estimates ranged from 3.0 to 52.7 hours, and mean, non-compartmentally derived values for total body clearance ranged from 11.6 to 24.0 L/hr/m^2; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding. With the 3-hour infusion increasing doses result in non-linear pharmacokinetics. For the 30% increase in dose from 135mg/m^2 to 175mg/m^2 the C_{max} and AUC_{0-t} values increased 75% and 81% respectively.
Intrapatient variability in systemic paclitaxel exposure was minimal. There was no evidence for accumulation of paclitaxel with multiple treatment courses.
In vitro studies of binding to human serum proteins indicate that 89-98% of drug is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.
The disposition of paclitaxel has not been fully elucidated in humans. Mean values for cumulative urinary recovery of unchanged drug have ranged from 1.3 to 12.6% of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome P450 enzymes. Following administration of a radiolabelled paclitaxel, an average of 26, 2, and 6% of the radioactivity was excreted in the faeces as 6alpha-hydroxypaclitaxel, 3'-p-dihydroxy-paclitaxel, 6a-3'-p-hydroxy-paclitaxel respectively. The formation of these hydroxylated metabolites is catalysed by CYP2C8, -3A4, and both – 2C8 and –3A4 respectively. The effect of renal or hepatic dysfunction on the disposition of paclitaxel following a 3-hour infusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of Paclitaxel 135mg/m^2 were within the range of those defined in non-dialysis patients.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polyoxyl castor oil and anhydrous ethanol.

6.2 Incompatibilities
The polyoxyl castor oil contained in Ebetaxel®/Paclitaxel "Ebewe" can result in DEHP [di(2-ethylhexyl)phthalate] leaching from plasticised polyvinylchloride (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.

6.3 Shelf life
3 years
Multiple use: contents of vial physically/chemically stable for 28 days after first withdrawal.
Administration to the patient: If Ebetaxel®/Paclitaxel "Ebewe" is diluted with 0.9% sodium chloride standard solution or 5% glucose standard solution, the prepared solution for infusion to be administered to the patient is physically/chemically stable for 48 hours when stored at 25°C, and must be administered via an in-line filter.

6.4 Special precautions for storage
Do not store above 25°C. Keep container in the outer carton, in order to protect from light.
Ebetaxel®/Paclitaxel "Ebewe" should not be frozen, since precipitations may develop. Such precipitations can be re-dissolved by re-heating the vial to 25°C (room temperature). A previously frozen vial has to discarded if the solution should remain turbid or cloudy and the precipitations cannot be re-dissolved. Freezing does not shorten the shelf life of Ebetaxel®/Paclitaxel "Ebewe".
The prepared solution for infusion to be administered to the patient does not need light protection.
The prepared solution for infusion to be administered to the patient should not be stored in a refrigerator, since precipitations may develop.
From a microbiological point of view, the product should be used immediately. If it is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.5 Nature and contents of container
White coloured vials of glass, Type I, Ph. Eur. The vials are placed in a cardboard carton.
1 vial containing 30mg/5ml of paclitaxel.
1 vial containing 100mg/16.7ml of paclitaxel.
1 vial containing 150mg/25ml of paclitaxel.
1 vial containing 210mg/35ml of paclitaxel.
1 vial containing 300mg/50ml of paclitaxel.

6.6 Instructions for use and handling <and disposal>
Handling: as with all antineoplastic agents, caution should be exercised when handling paclitaxel. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin and mucous membranes. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

Preparation for IV administration: Prior to infusion, Ebetaxel®/Paclitaxel "Ebewe" must be diluted, using aseptic techniques, in 0.9% Sodium Chloride Injection, or 5% Glucose Injection, or 5% Glucose and 0.9% Sodium Chloride Injection, to a final concentration of 0.3 to 1.2mg/mL. Solutions prepared for infusion are physically and chemically stable for up to 48 hours (including preparation and administration) at ambient temperature (approximately 25°C) and room lighting conditions. Diluted solutions should not be refrigerated.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Ebetaxel®/Paclitaxel "Ebewe" should be administered through an in-line filter with a microporous membrane ≤ 0.22µm. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.
To minimise patient exposure to DEHP, which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted Ebetaxel®/Paclitaxel "Ebewe" solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Disposal: All items used for preparation, administration or otherwise coming into contact with paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds.
Handle according to the guidelines for cytostatics.

7. MANUFACTURER

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A-4866 Unterach, AUSTRIA

8. DATE OF (PARTIAL) REVISION OF THE TEXT

October 2004