Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paclitaxel “Ebewe” 6mg/ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains 6mg Paclitaxel per 1 ml of concentrate for solution for infusion.

A vial of 5ml contains 30mg of Paclitaxel
A vial of 16.7ml contains 100mg of Paclitaxel
A vial of 25ml contains 150mg of Paclitaxel
A vial of 50ml contains 300mg of Paclitaxel

Excipients with known effects: Ethanol 96%; 403.66mg/ml and Macrogolglycerol Ricinoleate (Polyoxyl Castor Oil); 525.00mg/ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless or weakly yellow coloured solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ovarian cancer:
In first-line treatment of ovarian cancer, paclitaxel is indicated for the treatment, of patients with advanced disease or residual disease (>1 cm) after initial laparotomy in combination with cisplatin.

In second-line treatment chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum based therapy.

Breast cancer:
In the adjuvant setting, Paclitaxel “Ebewe” is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel “Ebewe” should be regarded as an alternative to extended AC therapy.

As a single agent. treatment of metastatic carcinoma of the breast in patients who have failed to respond adequately to standard treatment with anthracycline or in whom anthracycline therapy has not been appropriate.

Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable *(see sections 4.4 and 5.1)*

Advanced 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.

AIDS-related Kaposi's sarcoma: Paclitaxel is indicated for treatment of patients with advanced AIDS – related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy.

Limited efficacy data supports this indication; a summary of the relevant studies is shown in *section 5.1*.

4.2 Posology and method of administration

All patients must be pre-medicated with corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel "Ebewe" administration, in order to prevent severe hypersensitivity reactionse.g. Such pre-medication may consist of:.

Drug	**Dose**	**Administration prior to paclitaxel**
Dexamethasone	20 mg oral* or IV**	Approximately 12 and 6 hours for oral administration, 30-60minutes for IV
Diphenhydramine ***	50 mg IV	30 to 60 minutes
Cimetidine	300 mg IV	30 to 60 minutes
or ranitidine	50 mg IV	

* 8-20mg for Kaposi's Sarcoma
** intravenous
*** or an equivalent antihistamine eg chlorpheniramine 10 mg IV, administered 30 to 60 minutes prior to paclitaxel

Paclitaxel "Ebewe" should be administered through an in-line filter with a microporous membrane ≤0.22 microns (see *section 6.6).*

Given the possibility of extravasation, it is advisable to monitor closely the infusion site for possible infiltration during administration

Adults and elderly:
First-line treatment of ovarian cancer:
Although alternative medication regimes for paclitaxel are under investigation at [resent, a combination therapy of paclitaxel and cisplatin is recommended. Depending on the duration of infusion, two different dosages are recommended for paclitaxel treatment: 175 mg/m^2 of Paclitaxel "Ebewe" is administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 and the treatment is repeated at 3 week intervals or 135 mg/m^2 of Paclitaxel "Ebewe" is administered over 24 hours, followed by cisplatin 75 mg/m^2, the therapy is repeated with a 3 week interval between courses (see *section 4.5 & section 5.1)*

Second-line treatment of ovarian cancer:
The recommended dose of Paclitaxel "Ebewe" is 175 mg/m^2 administered over a period of 3 hours, with a 3 week interval between courses.

Adjuvant chemotherapy in breast cancer:
The recommended dose of Paclitaxel "Ebewe" is 175 mg/m^2 administered over a period of 3 hours every 3 weeks for four courses, following anthracycline and cyclophosphamide therapy.

First-line treatment of breast cancer:
When used in combination with doxorubicin (50 mg/m^2), Paclitaxel "Ebewe" should be administered 24 hours after doxorubicin. The recommended dose of Paclitaxel "Ebewe" is 220 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses ((see section 4.5 *& section 5.1*).

When used in combination with Trastuzumab, the recommended dose of Paclitaxel is 175 mg/m^2 administered intravenously over a period of three hours, with a three week interval between courses.

Paclitaxel “Ebewe” infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Second-line treatment of breast cancer:
The recommended dose of paclitaxel is 175 mg/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 175 mg/m^2 administered over a period of 3 hours, followed by cisplatin 80mg/m^2, with a 3 week interval between courses.

Treatment of AIDS-related Kaposi's sarcoma:
The recommended dose is 100 mg/m^2 administered over a period of 3 hours, with a two week interval between courses.

Subsequent doses of Paclitaxel “Ebewe” should be administered according to individual patient tolerance. Paclitaxel “Ebewe” should not be readministered until the neutrophil count is ≥ 1.5 x 10^9/L (≥1.0 x 10^9/L for KS patients) and the platelet count is ≥ 100 x 10^9/L (≥75 x 10^9/L for KS patients). Patients who experience severe neutropenia (neutrophil count <.5 x 10^9/L for a minimum of 7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients) (See *section 4.4*).

Special circumstances:

Patients with Hepatic Impairment:
There are no clinical trials in patients with insufficient hepatic function. Available data are not adequate to make a dose recommendation for patients with mild to moderate hepatic impairments (see *section 5.1 Pharmacokinetic properties*). Patients with severe hepatic impairment 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 *section 5.2*).

Use in children:
There are no clinical trials about efficacy and safety/undesirable effects in paediatric patients (under 18 years of age). Therefore, paclitaxel currently is not recommended for use in children.

4.3 Contraindications

Paclitaxel “Ebewe” 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 (See section 4.4 & 6.1).

Paclitaxel must not be used:

- during pregnancy and lactation *(see section 4.6).*
- in patients with baseline neutrophils <1.5 x 10^9/L (<1.0x 10^9/L for KS patients) or platelets <100 x 10^9/l (<75 x 10^9/l for KS patients).
- in KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections
- in patients with severe hepatic impairment

4.4 Special warnings and precautions for use

Paclitaxel should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Significant hypersensitivity reactions, characterised by dyspnoea and hypotension that requires treatment, angioedema and generalised urticaria have occurred in less than 1% of patients receiving Paclitaxel "Ebewe" after adequate premedication. These reactions are probably histamine-mediated. In case of severe hypersensitivity reactions Paclitaxel "Ebewe" infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug. Macrogolglycerol ricinoleate (polyoxyl castor oil), an excipient in this medicinal product, can cause these reactions. 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 "Ebewe" should be given before cisplatin when used in combination.

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 $\geq 1.5 \times 10^9$/L ($\geq 1.0 \times 10^9$/L for KS patients) and platelets recover to a level $\geq 100 \times 10^9$/L ($\geq 75 \times 10^9$/L for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

Severe cardiac conduction abnormalities have been reported rarely with single agent Paclitaxel "Ebewe". If patients develop significant conduction abnormalities during Paclitaxel "Ebewe" administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel "Ebewe".

Hypotension, hypertension, and bradycardia have been observed during Paclitaxel "Ebewe" administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of Paclitaxel "Ebewe" infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than in those with breast or ovarian carcinoma. A single case of heart failure which related to paclitaxel was seen in an AIDS-KS clinical study.

When Paclitaxel "Ebewe" is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with Paclitaxel "Ebewe" in these combinations, they should undergo baseline cardiac assessment including history, physical examination, echocardiogram, electrocardiogram (ECG) and/or multigated acquisition (MUGA) scan. Cardiac function should be monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/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 (eg every 1-2 cycles). *For more details see Summary of Product Characteristics of trastuzumab or doxorubicin.*

Although the occurrence of ***peripheral neuropathy*** is frequent, the development of severe symptoms is rare. If a patient should develop severe peripheral neuropathy, a dose reduction of 20% (25% for KS patients) is recommended for all subsequent courses of Paclitaxel "Ebewe". In NSCLC patients treated in the first-line setting, the administration of Paclitaxel "Ebewe" as a three hour infusion in combination with cisplatin resulted in a greater incidence of severe neurotoxicity than single agent Paclitaxel "Ebewe". In the first-line ovarian cancer patients, administration of paclitaxel as a 3-hour infusion combined with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of a combination of cyclophosphamide followed by cisplatin.

Hepatic Impairment:
Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression.

There is no evidence to suggest that the toxicity of Paclitaxel "Ebewe" is increased when given as a three-hour infusion to patients with mildly abnormal liver function. When Paclitaxel "Ebewe" is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment.

Patients should be monitored closely for the development of profound myelosuppression. Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments.

No data is available for patients with severe baseline cholestasis. Patients with severe hepatic impairment should not be treated with paclitaxel.

Pseudomembranous colitis has also been reported, rarely including cases in patients who have not received concurrent treatment 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.

The development of ***interstitial pneumonitis*** may be contributed to by Paclitaxel "Ebewe" in combination with radiation of the lung, irrespective of the order of treatment.

Paclitaxel has been shown to be a teratogen, embryotoxic and a mutagen in several experimental systems. Therefore female and male patients of reproductive age must take contraceptive measures for themselves and/or sexual partners during and for at least 6 months after therapy (see section 4.6). Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with paclitaxel.

Severe mucositis is rare in KS patients. If severe reactions occur, the paclitaxel dose should be reduced by 25%

This product contains approximately 50% ethanol (alcohol) by volume. i.e. up to 21 g per average dose, equivalent to 740 ml of a 3.5% vol beer, 190 ml of a 14% vol wine per dose. This may be harmful to patients suffering from alcoholism. It should also be taken into account when considering using this medicine in children and high risk groups such as in pregnant or breast-feeding women or patients with liver disease or epilepsy. The amount of alcohol you will receive per dose depends on your height and weight and the condition for which you are being treated. The amount of alcohol in this medicinal product may alter the effects of other medicines.

Since this product contains ethanol (403.66mg/ml) consideration should be given to possible CNS and other effects.

Special care should be taken to avoid intra-arterial application of Paclitaxel "Ebewe" (See section 4.5), since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.

Macrogolglycerol Ricinoleate (Polyoxyl Castor oil) may cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: During the administration of the recommended chemotherapy regimen for the first-line treatment of ovarian cancer, Paclitaxel "Ebewe" is to be given before cisplatin. When Paclitaxel "Ebewe" is given before cisplatin, the safety profile of Paclitaxel "Ebewe" 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. Patients treated with Paclitaxel "Ebewe" and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Doxorubicin: Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, Paclitaxel "Ebewe" for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see section 5.2).

Active substances metabolised in the liver: Caution should be exercised during concurrent administration of active substances which are metabolised in the liver as such active substances may inhibit the metabolism of paclitaxel. The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (See section 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6-alpha-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. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (eg erythromycin, fluoxetine, gemfibrozil) or induce (eg rifampicin, carbamazepine, phenytoin, phenobabrbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

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

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.

Reactions in road traffic and while operating machinery may be lowered. Alcohol may modify or increase the effect of other medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy
Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits (see also Section 5.3).
There is no adequate data from the use of paclitaxel in pregnant women, however as with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women. Paclitaxel should not be used during pregnancy unless the clinical condition of the woman requires treatment with paclitaxel.

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Paclitaxel “Ebewe” and to inform the treating physician immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraception for at least 6 months after treatment with paclitaxel.

Breast-feeding
It is not known whether paclitaxel is excreted in human milk. Paclitaxel “Ebewe” is contra-indicated during lactation. Breast feeding should be discontinued for the duration of paclitaxel therapy (see section 4.3).

Fertility
Paclitaxel “Ebewe” has been shown to be both embryotoxic and fetotoxic in rabbits and to decrease fertility in rats. (see also Section 5.3).

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

4.7 Effects on ability to drive and use machines

Paclitaxel “Ebewe” contains alcohol (see *List of excipients*); thus, Paclitaxel “Ebewe” administration may interfere with the ability to drive and use machines.

4.8 Undesirable effects

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

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

The most frequent significant undesirable effect was **bone marrow suppression**. Severe neutropenia (< 500 cells/mm³) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥ 7 days. Thrombocytopenia was reported in 11% of patients.
Three percent of patients had a platelet count nadir < 50,000/mm³ 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.

Neurotoxicity, mainly **peripheral neuropathy**, appeared to be more frequent and severe with a 175 mg/m^2 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m2 24-hour infusion (25% peripheral neuropathy, 3% severe) when Paclitaxel "Ebewe" was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with Paclitaxel "Ebewe" over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to Paclitaxel "Ebewe". Peripheral neuropathy was the cause of Paclitaxel "Ebewe" discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of Paclitaxel "Ebewe" discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for Paclitaxel "Ebewe" therapy.

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

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

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

In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

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

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); frequency cannot be estimated from the available data.

Infections and infestations:	*Very common*: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome *Uncommon:* septic shock *Rare*:* pneumonia, sepsis, peritonitis
Blood and the lymphatic system disorders:	*Very common* : myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, haemorrhages, *Rare**: febrile neutropenia

	Very rare:* acute myeloid leukaemia, myelodysplastic syndrome
Immune system disorders:	*Very common* : minor hypersensitivity reactions (mainly flushing and rash) *Uncommon* : significant hypersensitivity reactions requiring therapy (e.g. hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills,back pain, chest pain, tachycardia, abdominal pain, pain in extremity, diaphoresis, and hypertension) *Rare*:* anaphylactic reactions *Very rare**: anaphylatic shock
Metabolism and nutrition disorders:	*Very rare** : anorexia *Not known**: Tumour lysis syndrome
Psychiatric disorders:	*Very rare **: confusional state
Nervous system disorders:	*Very common* : neurotoxicity (mainly: peripheral neuropathy) *Rare*:* motor neuropathy (with resultant minor distal weakness) *Very rare** : autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders:	*Very rare*:* optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended *Not known**: Macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	*Very rare**: ototoxicity, hearing loss, tinnitus, Vertigo
Cardiac disorders:	*Common:* bradycardia *Uncommon* : cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction *Rare:* Cardiac failure *Very rare**: atrial fibrillation, supraventricular tachycardia
Vascular disorders:	*Very common* : hypotension *Uncommon:* hypertension, thrombosis, thrombophlebitis *Very rare **: shock *Not known**: Phlebitis
Respiratory, thoracic and mediastinal disorders:	*Rare*:* dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure *Very rare**: cough
Gastrointestinal disorders:	*Very common* : nausea, vomiting, diarrhoea, mucosal inflammation *Rare*:* bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis

	Very rare* mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, , neutropenic colitis
Hepato-biliary disorders:	*Very rare*:* hepatic necrosis, hepatic Encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	*Very common* : alopecia *Common:* transient and mild nail and skin changes *Rare*:* pruritus, rash, erythema *Very rare**: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) *Not known**: Scleroderma
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 localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) *Rare*:* malaise, asthenia, pyrexia, dehydration, oedema
Investigations:	*Common* : severe elevation in aspartate aminotransferase (AST), serm glutamic oxaloacetic transaminase (SGOT), severe elevation in alkaline phosphatase *Uncommon:* severe elevation in bilirubin *Rare**: increase in blood creatinine

Concerning Infections: cases with lethal outcome have been reported.
Concerning Hepatobiliary disorders: cases with fatal outcome have been reported.

Breast cancer patients who received Paclitaxel in the adjuvant setting following AC experienced more neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infection, fever, nausea/vomiting and diarrhoea than patients who received AC alone. However, the frequency of these events was consistent with the use of single agent Paclitaxel “Ebewe”, as reported above.

Combination treatment
The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (Paclitaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (Paclitaxel “Ebewe” + doxorubicin: 267 patients), and another investigating the combination with trastuzumab (planned subgroup analysis, paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (Paclitaxel “Ebewe” + cisplatin: over 360 patients*) (see section 5.1).*

When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with Paclitaxel “Ebewe” followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with Paclitaxel “Ebewe” as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/ myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when Paclitaxel "Ebewe" (220 mg/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²).

Nausea and vomiting appeared to be less frequent and severe with the Paclitaxel "Ebewe" (220 mg/m²) / doxorubicin (50 mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the Paclitaxel "Ebewe"/doxorubicin arm.

When Paclitaxel "Ebewe" 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 "Ebewe" or trastuzumab) were reported more frequently than with single agent Paclitaxel "Ebewe": heart failure (8% vs 1%), infection (46% vs 27%), chills (42% vs 4%), fever (47% vs 23%), cough (42% vs 22%), rash (39% vs 18%), arthralgia (37% vs 21%), tachycardia (12% vs 4%),diarrhoea (45% vs 30%), hypertonia (11% vs 3%), epistaxis (18% vs 4%), acne (11% vs 3%), herpes simplex (12% vs 3%), accidental injury (13% vs 3%), insomnia (25% vs 13%), rhinitis (22% vs 5%), sinusitis (21% vs 7%), and injection site reaction (7% vs 1%). Some of these frequency differences may be due to the increased number and duration of treatments with Paclitaxel "Ebewe"/trastuzumab combination vs single agent Paclitaxel "Ebewe". Severe events were reported at similar rates for Paclitaxel "Ebewe"/trastuzumab and single agent Paclitaxel "Ebewe".

When doxorubicin was administered in combination with Paclitaxel "Ebewe" in metastatic breast cancer, cardiac contraction abnormalities (≥20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. Congestive heart failure was observed in < 1% in both Paclitaxel "Ebewe"/doxorubicin and standard FAC arms.

Administration of trastuzumab in combination with Paclitaxel "Ebewe" in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with Paclitaxel "Ebewe" single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment.

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between KS patients and patients treated with paclitaxel monotherapy for other solid tumours, based on a clinical study including 107 patients.

Blood and the lymphatic system disorders: bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia ($<0.5 \times 10^9$ cells/L) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥ 7 days was 22%.

Neutropenic fever related to paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.

Thrombocytopenia was observed in 50% of patients, and was severe ($< 50 \times 10^9$ cells/L) in 9%. Only 14% experienced a drop in their platelet count $< 75 \times 10^9$ cells/L, at least once while on treatment.

Bleeding episodes related to paclitaxel were reported in < 3% of patients, but the haemorrhagic episodes were localised. Anaemia (Hb < 11 g/dL) was observed in 61% of patients and was severe (Hb < 8 g/dL) in 10%. Red cell transfusions were required in 21% of patients.

Hepato-biliary disorders: Among patients (> 50% on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail:medsafety@hpra.ie

4.9 Overdose

There is no known antidote for Paclitaxel "Ebewe" overdose. In the case of overdose, the patient should be closely monitored. The first possible complications of an overdose would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Treatment should be directed at these primary toxicities.
Overdoses in paediatric patients may be associated with acute ethanol toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: cytostatic agent,
ATC code: L01C D01

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization.
This stability results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of Paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m^2 / cisplatin 75 mg/m^2) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II$_{b-c}$, III or IV primary ovarian cancer received a maximum of 9 treatment courses of Paclitaxel (175 mg/m^2 over 3 hr) followed by cisplatin (75 mg/m^2) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either Paclitaxel (135mg/m² over 24 hrs) followed by cisplatin (75 mg/m²) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residual disease after staging laparotomy, or with distant metastases.
While the two different Paclitaxel posologies were not compared with each other directly, in both trials patients treated with Paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy.

Increased neurotoxicity arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion Paclitaxel /cisplatin as compared to patients who received cyclophosphamide/cisplatin.

In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-233). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p =0.0014), and a significant reduction of 19% in the risk of death (p =0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95%CI: 0.78-1.07). However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles.

It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomised to receive or not four courses of paclitaxel at a higher dose of 225 mg/ m2 following four courses of AC (NSABP B-28, BMS CA139-270).At a median follow-up of 64 months, paclitaxel patients has a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006); paclitaxel treatment was associated with a reduction in the risk of death of 7% (95% CI: 0.78-1.12). All subset analyses favoured the paclitaxel arm. In this study patients with hormone receptor positive tumor had a reduction in the risk of disease recurrence of 23% (95% CI: 0.06-0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95% CI: 0.7-1.11).

In the first-line treatment of metastatic breast cancer, the efficacy and safety of Paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials.
In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m²) followed after 24 hours by Paclitaxel (220 mg/m² by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²), both administered every three weeks for eight courses.

In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of Paclitaxel /doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the Paclitaxel /doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of the Paclitaxel and trastuzumab combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and Paclitaxel (175 mg/m²) 3-hour infusion, every three weeks was compared to single agent.

Paclitaxel (175 mg/m²) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the Paclitaxel /trastuzumab combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to Paclitaxel alone. The most significant toxicity observed with the Paclitaxel /trastuzumab combination was cardiac dysfunction *(see 4.8).*

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

In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines.

This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (CI 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent after the first 3 cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least 2 months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.

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 135 mg/m^2 to 175 mg/m^2 the C_{max} and AUC ($_{0-\infty}$) values increased 75% and 81% respectively.

Intra-patient 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, rantidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.
The distribution and metabolism of paclitaxel in humans has not been fully investigated. The cumulative excretion of unchanged paclitaxel has ranged from 1.3 to 12.6% of the dose on average, which is an indication of extensive non-renal clearance.

Hepatic metabolism and biliary clearance may be the principal mechanism for elimination of paclitaxel. Paclitaxel appears to be metabolised primarily by cytochrome CP450 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 metabolitesis catalysed by CYP2C8 & CYP 3A4, and both CYP 2C8 and CYP 3A4 respectively.
The effect of renal or hepatic dysfunction on the elimination of paclitaxel following a 3-hourinfusion has not been investigated formally. Pharmacokinetic parameters obtained from one patient undergoing haemodialysis who received a 3-hour infusion of Paclitaxel 135 mg/m^2 were within the range of those defined in non-dialysis patients.

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

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

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

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

Anhydrous citric acid
Macrogolglycerol Ricinoleate
Ethanol 96%

6.2 Incompatibilities

The macrogolglycerol ricinoleate contained in 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.

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

6.3 Shelf life

2 years.

After first opening: Chemical and physical stability has been demonstrated for up to 28 days when stored below 25^{o}C. Other in-use storage times and conditions are the responsibility of the user.

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.

After dilution: 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 precipitates may develop.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at room temperature for 48 hours and 2-8°C for 14 days when diluted in 0.9% Sodium Chloride Injection or 5% Dextrose solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze
Keep container in the outer carton in order to protect from light

After first opening: *See section 6.3*
After dilution: *See section 6.3*

6.5 Nature and contents of container

White coloured Type I glass vials with a flouropolymer-coated halobutyl rubber stopper in a cardboard carton

Vial sizes: 5ml, 16.7ml, 25ml and 50ml.
Each box contains one vial.

Not all vial sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Handling: as with all antineoplastic agents, caution should be exercised when handling Paclitaxel "Ebewe". 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.

If unopened vials are refrigerated, a precipitate may form that redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

The Chemo-Dispensing Pin device or similar devices with spikes should not be used since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Pregnant staff should be excluded from working with this product.

Preparation for IV administration: prior to infusion, Paclitaxel "Ebewe" must be diluted using aseptic techniques in 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, or 5% Dextrose and 0.9% Sodium Chloride Injection to a final concentration of 0.3 to 1.2 mg/ml.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. However, haziness does not affect the potency of the product.

Paclitaxel "Ebewe" solutions should be administered through an in-line filter with a microporous membrane $\leq$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.

There have been rare reports of precipitation during Paclitaxel "Ebewe" infusions, usually towards the end of a 24 hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, Paclitaxel "Ebewe" should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

To minimise patient exposure to DEHP which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted 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 (e.g. IVEX-2®) 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 "Ebewe" should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7 MARKETING AUTHORISATION HOLDER

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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