Package leaflet: Information for the user
Paclitaxel "Ebewe" 6mg/ml Concentrate for Solution for Infusion

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Paclitaxel "Ebewe" 6mg/ml is and what it is used for

Paclitaxel "Ebewe" 6mg/ml concentre for solution for infusion contains the active substance paclitaxel. Paclitaxel "Ebewe" 6mgml belongs to a group of compounds called "taxanes" which are anticancer agents.
Paclitaxel "Ebewe" 6mg/ml is used for treatment of:

- Ovarian cancer either as an initial therapy in combination with the platinum-containing medicine, cisplatin, or as a second-line treatment when other platinum-containing treatments have not worked;
- Breast cancer in patients who have not responded to standard treatment using a medicine belonging to the group known as anthracyclines, or for whom such treatment should not be used;
- Non-small cell lung cancer, in combination with cisplatin, in patients who are not candidates for potentially curative surgery and/or radiotherapy;
- Paclitaxel is indicated for treatment of patients with advanced AIDS – related Kaposi's sarcoma who have failed prior liposomal anthracycline therapy.

2. What you need to know before you use Paclitaxel "Ebewe" 6mg/ml

<u>You should not be given Paclitaxel "Ebewe" 6mg/ml:</u>

- If you are hypersensitive (allergic) to paclitaxel, or to any of the other ingredients of Paclitaxel "Ebewe", especially polyoxyl castor oil (Macrogolglycerol Ricinoleate) as polyoxyl castor oil may cause severe allergic reactions
- If you are pregnant and/ or breast-feeding

- If your white blood cell or platelet count is very low. Your doctor will have checked the results of your last blood test to ensure you can receive your course of treatment.
- In patients with Kaposi Syndrome, Paclitaxel "Ebewe" should not be used if you have concurrent, serious, uncontrolled infections.
- If you have severe liver disease
- If you are under 18 years of age

Warnings and precautions:

Talk to your doctor or pharmacist before using Paclitaxel "Ebewe" 6mg/ml

- If you notice marked allergic reaction this may cause shortness of breath, dizziness (caused by low blood pressure), swelling of the face or rash
- If you have heart disease or liver problems (if liver damage is severe, you should not be given paclitaxel)
- If your blood cell counts are abnormal
- If you experience irregular heartbeats, dizziness or faintness during treatment
- If you experience tingling, burning or numbness in your fingers and/or toes
- If this product is given to you along with radiation treatment (radiotherapy) of the lungs (see section 4. Possible side effects)
- If diarrhoea occurs during or shortly after treatment with this product as your colon could be inflamed
- If you have Kaposi's sarcoma and have a sore or inflamed mouth
- This product is not recommended for use in children under 18 years
- If you planning on becoming pregnant
- If you suffer from alcoholism as this product contains alcohol

Take special care with Paclitaxel "Ebewe" 6mg/ml:

- You will be asked to take a steroid tablet approximately 12 hours and 6 hours before receiving Paclitaxel "Ebewe" 6mg/ml. You will also be given injections of antihistamines and H2 antagonists approximately 30–60 minutes before you receive Paclitaxel "Ebewe" 6mg/ml. These will minimise certain undesirable effects, such as allergic reactions, which may occur after the infusion of Paclitaxel "Ebewe".
- Paclitaxel "Ebewe" should be given before cisplatin, when used in combination.

Children and adolescents
The safety and effectiveness of Paclitaxel "Ebewe" 6mg/ml in children has not been established. **Paclitaxel "Ebewe" 6mg/ml** is not recommended for children and adolescents under the age of 18 years.

Other medicines and Paclitaxel "Ebewe" 6mg/ml
Please inform your hospital specialist if you are taking or have recently taken any other medicines, even those not prescribed.

Special care should be taken if you are taking other medicinal products which could interact with paclitaxel.

The following drugs may increase the level of paclitaxel in the blood:

- erythromycin (antibiotic)
- fluoxetine (used to treat nervous disorders such as depression)
- gemfibrozil (used to prevent heart disease)
- nelfinavir and ritonavir (antiviral treatments for HIV/AIDS infection)

The following drugs may decrease the level of paclitaxel in the blood:

- rifampicin (antibiotic)
- carbamazepine, phenytoin and phenobarbital (used to control epilepsy)
- efavirenz and nevirapine (antiviral treatments for HIV/AIDS infection)

Paclitaxel "Ebewe" 6mg/ml with food and drink and alcohol
Paclitaxel can be given together with food and drink. However, you should check with your doctor whether drinking alcohol is advisable for you during treatment with Paclitaxel. Alcohol may modify or increase the effect of other medicines. Paclitaxel "Ebewe" contains alcohol (For more information on the alcohol content please see the end of section 2). The amount of alcohol you will receive per dose depends on your height and weight and the condition for which you are being treated. Alcohol may modify or increase the effect of other medicines.

Pregnancy and breast-feeding
Pregnancy
Paclitaxel should not be used during pregnancy unless clearly advised. Please inform your hospital specialist if you are pregnant or planning to become pregnant.

This medicine may cause birth defects, therefore, you must not become pregnant during treatment with paclitaxel and you and/or your partner must use an effective method of contraception whilst you are receiving treatment with paclitaxel and for six months after treatment has finished. If pregnancy occurs during treatment, or within the six months after treatment has finished, inform your doctor immediately. Paclitaxel may have an anti-fertility effect which could be irreversible. Male patients are therefore advised to seek advice on conservation of sperm prior to treatment.

Breast-feeding
You should not breast-feed whilst you are being treated with Paclitaxel "Ebewe" 6mg/ml. Do not begin breast-feeding again until your doctor tells you that it is safe to do so.
Ask your hospital specialist for advice before taking any medicine.

Driving and using machines:
Paclitaxel "Ebewe" 6mg/ml contains some alcohol, therefore it may be unwise to drive immediately after a course of treatment. Reactions in road traffic and while operating machinery may be lowered. In addition, some side effects such as dizziness, nausea or tiredness may affect your ability to drive or operate machinery.

Paclitaxel "Ebewe" 6mg/ml contains **Ethanol,** approximately 50% ethanol a form of alcohol and **Polyoxyl Castor Oil**
Polyoxyl Castor Oil May cause severe allergic reactions. This medicinal product contains 50 vol % ethanol (alcohol), i.e. up to 21 mg per dose, equivalent to 740 ml of a 3.5% vol beer, 190 ml of a 14% vol wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy. Please see applicable sections for warnings relating to alcohol located in the above sections.

3. How to use Paclitaxel "Ebewe" 6mg/ml

Adults and the Elderly:
Your treatment will usually be given to you in hospital. Paclitaxel will be given under supervision of a doctor, who can give you more information.

Before you receive your paclitaxel injection you will be given other medicines to prevent allergic reactions (a corticosteroid, e.g. dexamethasone, an antihistamine, e.g.diphenhydramine and an H2-receptor antagonist, e.g. cimetidine or ranitidine).

Paclitaxel may be given alone or in combination with other anti-cancer medicines. Your doctor will decide on the dose of product you should have and how many doses you will be given. If you are receiving combination treatment with paclitaxel and cisplatin, the paclitaxel should be administered before the cisplatin in order to reduce the possibility of side effects. If you are receiving combination treatment with paclitaxel and doxorubicin, the paclitaxel should be administered 24 hours after doxorubicin.

You will be given paclitaxel as an infusion (slow injection via a drip) into a vein. Tell your doctor or nurse at once if you notice any pain at the injection site during or shortly after treatment. Pain around the injection site could mean the needle has not been properly inserted into the vein.

The dose of paclitaxel will depend on the illness for which you are being treated, the results of your blood tests and any side effects you have had to previous doses. The dose also depends on your body surface area (expressed as mg/m2) which is calculated from your height and weight. Depending on your illness, dosing is typically between 100 mg/m2 and 220 mg/m2 of paclitaxel given over 3 or 24 hours and repeated every two or three weeks. As paclitaxel is most likely to be given to you in hospital, under the supervision of a doctor, it is unlikely that you will receive an incorrect dose. However if you have any concerns about the dose you receive, please tell your doctor.

4. Possible side effects

Like all medicines, Paclitaxel "Ebewe" 6mg/ml can have side effects, although not everybody gets them.
Your doctor will discuss these with you and will explain the risks and benefits of your treatment. If you experience any of the following side effects tell your doctor. You may need urgent medical attention or hospitalisation immediately.

Uncommon side-effects which may affect more than 1 person in 1000 are listed below:

- Severe chest pains possibly radiating to the jaw or arm, sweating, breathlessness and nausea (heart attack)
- Severe infection including sepsis (blood poisoning) with a state of shock
- Feeling unusually hot or cold (fever or chills)
- Blood clots in the veins (thrombosis) and inflammation of the veins associated with blood clots (thrombophlebitis) – this may present as pain and/or swelling in your arms or legs or inflammation of the vein
- Severe allergic reactions causing low or high blood pressure, chest pain, breathing problems, fast heart-beat (pulse), pain in your abdomen or extremities, sweating, severe itching and/or back pain.

Rare side-effects which may affect less than 1 person in 1000 are listed below:

- Severe allergic reaction (anaphylactic reaction): you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- Shortness of breath, cough, coughing up blood or pain in the chest or shoulder (eg pulmonary embolism). Some of these effects may not occur immediately (lung fibrosis)

Very Rare side-effects which may affect less than 1 person in 10000 are listed below:

- Life-threatening allergic reaction (anaphylactic shock)
- Seizures ('fits')
- Rapid formation of a rash followed by the appearance of skin lesions on the soles of the feet and palms and ulcers in the mouth (erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis). Severe skin peeling (exfoliative dermatitis)
- Persistent diarrhoea

<u>Tell your doctor as soon as possible if you notice any of the following:</u>

Very Common side-effects which may affect more than 1 person in 10 are listed below:

- Joint or muscle weakness, pain, aching or loss of sensation in the limbs. These usually reduce or disappear several months after stopping treatment with paclitaxel
- Infection – usually of the urinary tract or upper respiratory tract. This may be associated with low blood cell count resulting from receiving Paclitaxel. This can sometimes be fatal.
- Bone marrow suppression, which can lead to decreased blood cell counts and may result in infections, anaemia with paleness and weakness, and bruising and bleeding
- Low blood pressure which may cause you to feel light-headed, particularly when standing up
- Pain in the muscle or joints
- Hair loss
- Nausea and vomiting

- Mild diarrhoea
- Soreness of the mouth or tongue
- Mild allergic reactions including flushing and skin rash
- Nerve problems – these may appear as pins and needles in the hands and feet

Common side-effects which may affect more than 1 person in 100 are listed below:

- Slow heart-beat
- Injection site reactions (local swelling, pain, redness, hardening of tissues, death of skin tissue, extravasation (leaking of drug outside the vein) resulting in cellulitis (painful
- swelling and redness)
- Temporary mild changes to the nails and skin

Uncommon side-effects which may affect more than 1 person in 1000 are listed below:

- Irregular heartbeats
- Fainting
- High blood pressure (may give you headaches)
- Yellowing of whites of eyes and skin
- Pain in the middle of your chest which may be caused by heart disease
- Pain or weakness in heart muscles (heart muscle degeneration)
- Irregular heartbeat (may be caused by irregular impulse conduction)

Rare side-effects which may affect less than 1 person in 1000 are listed below:

- Pneumonia
- Effect on nerves that control the muscles, resulting in muscle weakness in arms and legs
- (motor neuropathy)
- Itching, skin rash/redness
- Accumulation of fluid in the whole body (oedema)
- Dehydration
- Loss of energy
- Problems with your lungs such as inflammation or accumulation of fluids, which may make it difficult to breathe
- Abdominal pain caused by inflammation in your bowel, bowel obstruction or perforation of the wall of your bowel
- Inflammation of your pancreas (pancreatitis)
- Heart failure
- A feeling of discomfort or uneasiness

Very Rare side-effects which may affect less than 1 person in 10000 are listed below:

- Increased frequency of heartbeat
- Nettle rash (urticaria)
- Effect on the brain (encephalopathy)
- Damage to the liver which may be severe (hepatic necrosis). This may have an effect on brain function (hepatic encephalopathy). This can sometimes be fatal.
- Loss of hearing or ringing in the ears
- Balance problems
- Visual disturbances

- Staggering when walking
- Dizziness
- Headache
- Constipation
- Abdominal pain which may be caused by accumulation of fluid in the abdomen (ascites), inflammation in your gut or blood clot in the blood vessels to your bowel
- Loss of appetite
- Confusion
- Shock
- Loosening of finger or toe nails (you are advised to wear protection on your hands and feet when exposed to the sun)
- Heartburn, nausea and/or vomiting which may be caused by inflammation of the gullet
- Cough
- Muscle weakness, cramps, severe bowel or abdominal pain or dizziness when standing up which may be caused by a disease of the nervous system
- Acute leukaemia (blood cancer) or related condition (myelodysplastic syndrome) which your doctor will check for

Other side-effects with unknown frequency are listed below:
- A condition called tumour lysis syndrome which may cause high levels of sodium or
- potassium or low levels of calcium in your blood
- A swelling of part of the back of your eye (macular oedema)
- Visual disturbances such as seeing flashes of light (photopsia) or floaters
- Disease of your connective tissue (scleroderma)
- An autoimmune disorder that may affect your skin, joints, kidneys, brain, and other organs (systemic lupus erythematosus)

Like many other anti-cancer medicines, paclitaxel may cause sterility, which could be permanent.

Paclitaxel may cause inflammation of the lungs when used in combination with, or after, radiotherapy.

Laboratory tests (eg blood tests) may be performed to check for changes in liver activity, kidney function and blood cells, which are side effects of paclitaxel treatment.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

Reporting of side effects
You can also report side effects directly via: HPRA Pharmacovigilance, Earlsfort Terrace IRL – Dublin 2 Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.hpra.ie E-mail: medsafety@hpra.ie

By reporting any side effects you can help provide more information on the safety of this medicine.

5. How to store Paclitaxel “Ebewe” 6mg/ml

This medicine will be stored in the hospital pharmacy and made up in a special area before the doctor or nurse gives it to you.
Keep out of the sight and reach of children
Do not use this medicine after the expiry date which is stated on the carton and vial The expiry date refers to the last day of that month.
Do not store above 25°C. Do not freeze
Keep container in the outer carton in order to protect from light.
Do not use this medicine if you notice signs of deterioration, such as carton discoloration

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

Paclitaxel "Ebewe" 6mg/ml is available in vial sizes of 5ml, 16.7ml, 25ml and 50ml. Each box contains 1 vial

The other ingredients are Macrogolglycerol Ricinoleate (Polyoxyl Castor Oil), ethanol and citric acid.

Paclitaxel "Ebewe" 6mg/ml is supplied as a concentrate in vials containing 30 mg or 100mg or150mg or 300mg paclitaxel.

This concentration has to be diluted in a solution before being given to you as an intravenous injection. The final solution for injection contains 0.3 – 1.2mg/ml of Paclitaxel "Ebewe".

Marketing Authorisation Holder:
Fannin LTD., Fannin House, South County Business Park, Leopardstown, Dublin 18, Ireland

Manufacturer responsible for batch release:
Ebewe Pharma Ges.m.b.h.Nfg.KG
A-4866 Unterach, Austria.

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The following information is intended for medical or healthcare professionals only:
Below is a summary of information to assist in the preparation of Paclitaxel "Ebewe" 6mg/ml. You should be experienced in the handling and use of cytotoxic agents and be familiar with the Summary of Product Characteristics for Paclitaxel "Ebewe" 6mg/ml. Reference should be made to guidelines on the safe use and handling of antineoplastic agents.
Preparation, storage and administration should be carried out in non-PVC containing equipment.

Storage

The unopened vials may be stored at room temperature and protected from light.
Do not store above 25°C. Do not freeze.

After first opening: Chemical and physical stability has been demonstrated for up to 28 days when stored below 25°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.
Paclitaxel "Ebewe" 6mg/ml must be diluted under aseptic conditions to a concentration of 0.3 to 1.2mg/ml with one of the following: 0.9% Sodium Chloride Intravenous Infusion, 5% Glucose Intravenous Infusion or 0.9% Sodium Chloride and 5% Glucose Intravenous Infusion.
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.
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.

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.

Administration and dosage:
All patients should be pre-medicated with corticosteroids, antihistamines and H2 antagonists prior to administration. The diluted Paclitaxel infusion should be administered using non-PVC containing equipment through an in-line filter with a microporous membrane <0.22µm.

The recommended doses for the intravenous infusion are as follows:
First-line ovarian cancer: 175mg/m2 administered over 3 hours followed by cisplatin at a dose of 75mg/m2 or 135mg/m2 over 24 hours followed by cisplatin 75mg/m2;
Second-line ovarian cancer and breast cancer: 175mg/m2 over 3 hours;
Non-small cell lung cancer: 175mg/m2 over 3 hours followed by cisplatin 80mg/m2 Karposi sarcoma: 100mg/m2 over 3 hours.

There should be a 3 week interval between courses dependent upon patient tolerance. Paclitaxel "Ebewe" 6mg/ml should not be re-administered until the neutrophil count is ≥1.5x109/l (≥1.0 x 109/L for KS patients) and the platelet count is ≥100x109/l (≥75 x 109/L for KS patients). Patients experiencing severe neutropenia or severe peripheral neuropathy should be subjected to a dose reduction of 20% for subsequent courses (25% for KS patients).