Package leaflet: Information for the user

Paclitaxel 6 mg/ ml concentrate for solution for infusion
paclitaxel

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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Paclitaxel is and what it is used for

The name of your medicine is 'Paclitaxel 6 mg/ ml concentrate for solution for infusion' but in the rest of leaflet it will be called 'Paclitaxel'. Paclitaxel is available as vials containing 30 mg, 100 mg, or 300 mg paclitaxel in a 6 mg/ml solution which has to be diluted before being given to you.

This medicine belongs to a group of anti-cancer medicines called taxanes. These agents inhibit the growth of cancer cells.

Paclitaxel is used to treat*:*

Ovarian cancer:

- as first therapy (after initial surgery in combination with the platinum-containing medicine cisplatin)
- after standard platinum-containing medicines have been tried but did not work.

Breast cancer:

- as first therapy for advanced disease or disease which has spred to other parts of the body (metastatic disease). Paclitaxel is either in combination with an anthracyclines (e.g. doxorubicin) or with a medicine called trastuzumab (for patients for whom anthracycline is not suitable and whose cancer cells have a protein on their surface called HER2, see package of trastuzumab).
- after initial surgery following treatment with anthracycline and cyclophosphamide (AC) as an additional treatment.
- As second-line treatment for patients who have not responded to standard treatments using anthracyclines, or for whom such treatment should not be used.

Advanced non-small cell lung cancer*:*

- in combination with cisplatin, when surgery and/or radiation therapy aren't suitable.

AIDs-related Kaposi's sarcoma:

- where other treatments (i.e. liposomal anthracyclines) has been tried but did not work.

2. What you need to know before you use Paclitaxel

Do not use Paclitaxel

- if you are allergic (hypersensitivity) to paclitaxel or any other ingredients of this medicine (listed in section 6), especially macrogolglycerol ricinoleate
- if you are breast-feeding
- if you have too few white blood cells count (baseline neutrophil counts < 1.5 x 10^9/l - your doctor will advise you on this) in your blood . Your doctor will take blood samples to check this
- if you have a serious and uncontrolled infection and Paclitaxel is to be given for the treatment of Kaposi's sarcoma.
- if any of these apply to you, talk to your doctor or pharmacist before starting treatment with Paclitaxel.

Warnings and precuations

Talk to your doctor, pharmacist or nurse before using Paclitaxel. Take special care with Paclitaxel.

- if you have heart conduction problems
- if you have severe liver problems; in this case the use of Paclitaxel is not recommended.
- if you develop severe or persistent diarrhoea, with fever and stomach pain, during or shortly after the treatment with paclitaxel. Your colon could be inflamed (pseudomenbranous colitis)
- if you have a sore or red mouth (signs of mucositis) and are treated for Kaposi's sarcoma. You may need a lower dose
- if you have numbness, tingling, pricking sensations, sensitivity to touch, or weakness of the arms and legs (sign of peripheral neuropathy); a dose reduction of Paclitaxel may be necessary.
- if you had previous radiation to your chest (because it may increase the risk of lung inflammation)
- if you experience **severe allergic reactions** (for example difficulty breathing, shortness of breath, chest tightness, drop in blood pressure, dizziness, light headedness, skin reactions such as rash or swelling).
- if you have **fever, severe chills, sore throat or mouth ulcers** (signs of bone marrow suppression).

It is important to tell the doctor about any of your medical conditions, whether they are included in the above lists or not. Please tell your doctor if you are taking, or have recently taken, any other medicines, including ones that are not prescribed for you.

Children

Paclitaxel is not recommended for use in children (under 18 years).

Other medicines and paclitaxel

Tell your doctor if you are taking, have recently taken or might take any other medicines
Interaction means that different medicines may influence each other. Interaction may occur and your

doctor needs to know when using Paclitaxel together with:

- cisplatin (to treat cancer): Paclitaxel must be given before cisplatin. Your renal function may need to be checked more frequently.
- doxorubicin (to treat cancer): Paclitaxel must be administered 24 hours after doxorubicin, to avoid high level of doxorubicine in your body.
- efavirenz, nevirapine, ritonavir, nelfinavir, or other protease-inhibitors, which are **HIV treatments.** A dose adjustment of Paclitaxel may be necessary.
- erythromycin, an **antibiotic,** fluoxetine, an **antidepressant** or gemfibrozil, used for **lowering cholesterol.**

A dose reduction of Paclitaxel may be necessary.

- rifampicin, an **antibiotic used for tuberculosis.** A dose increase of Paclitaxel may be necessary.
- carbamazepine, phenytoin or phenobarbital, used for **epilepsy.**

Paclitaxel with food, drink and alcohol

Paclitaxel is unaffected by food and drink.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If there is a chance that you could become pregnant, **use an effective and safe method of contraception during treatment**. Paclitaxel should not be used during pregnancy unless clearly necessary. Female and male patients of fertile age, and/or their partners should use contraceptions for at least 6 months after treatment with paclitaxel. Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of irreversible infertility.

If you are breast-feeding, tell your doctor. It is not known if paclitaxel passes into breast milk. Because of the possibility of harm to the infant stop breast-feeding if you are taking Paclitaxel. Do not restart breast-feeding unless your doctor has allowed you to**.**

Driving and using machines

There is no reason why you cannot continue driving between courses of paclitaxel but you should remember that this medicine contains some alcohol and it may be unwise to drive or use machines immediately after a course of treatment. As in all cases, you should not drive or use machines if you feel dizzy or light-headed.

Paclitaxel contains macrogolglycerol ricinolate and ethanol

This medicinal product contains macrogolglycerol ricinolate **(**polyoxyl castor oil) that may cause severe allergic reactions. If you are allergic to castor oil, talk to your doctor before you receive Paclitaxel.

This medicinal product also contains 49.7 % vol ethanol (alcohol), i.e. up to 21 g (19.5 g) per average dose, equivalent to 740 ml (687 ml) of a 3.5 % vol beer, 190 ml (176.4) 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 those with liver disease or epilepsy. The alcohol in this medicine may also affect the way other medicines work.

3. How to use Paclitaxel

If you are prescribed Paclitaxel, it will be given to you by doctors or nurses experienced in giving chemotherapy.

Paclitaxel will normally be given to you by a doctor or a nurse through a drip (infusion) into a vein. Your doctor will decide what dose to give and the number of days treatment you will receive depending upon your condition. The dose you receive will be based on your body surface area and the result of blood tests carried out before treatment. The usual dose is 175 mg/m^2, body surface area, given over 3 hours followed by the cisplatin for ovarian and lung cancer. You will also receive cisplatin after paclitaxel if you are being treated for lung cancer. For breast cancer recommended dose is 175 mg/m² administered over 3 hours following therapy with anthracycline and cyclophosphamide. When used in combination with doxorubicin paclitaxel will be administered 24 hours after doxorubicin at a dose of 220 mg/m^2. The timing of paclitaxel administration after trastuzumab will depend on how you react to this medicine.

If you are given more Paclitaxel than you should

Your dose will be carefully calculated by the doctors, so overdose is unlikely. However, iftoo much is given this is likely to make the usual side effects worse, particularly blood disorders, numbness/tingling especially of the arms, hands, legs or feet and stomach upsets including vomiting and diarrhoea.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any signs of allergic reactions. These may include one or more of the following:

- flushing,
- skin reactions,
- itching,
- chest tightness,
- shortness or difficulty in breathing,
- swelling.

These can all be signs of serious side effects.

Tell your doctor immediately:

- If you have sore throat or mouth ulcer, severe chills and high temperature (signs of bone marrow suppression).
- If you have numbness or weakness of the arms and legs (signs of peripheral neuropathy).
- If you develop severe or persistent diarrhoea, with fever and stomach pain.

Other known side effects are

Very common (may affect more than 1 in 10 people):

- an effect on the bone marrow, which can cause decreased numbers of some blood cells. This may cause anaemia. It can also lead to infections, mainly urinary tract and upper respiratory tract infections with reported cases of fatal outcome pain, redness or swelling at the injection site
- tests may show: decreased number of blood platelet count, white or red blood cells count and bleeding
- milder allergic (hypersensitivity) reactions, such as flushing and rash
- nerve problems affecting the hands and or feet (peripheral neuropathy), which can cause tingling feelings in the skin, numbness and/or pain
- low blood pressure
- feeling sick (nausea), being sick (vomiting) and diarrhoea
- hair loss
- muscle or joint pain
- inflammation of areas such as the lining of the mouth.

Common (may affect up to 1 in 10 people):

- slow heart beat (pulse)
- mild changes in nail and skin which soon disappear
- painful swelling and inflammation where the injection is given which may cause tissue hardening (occasionally cellulitis, thickening and scarring of the skin (skin fibrosis), death of skin cells(skin necrosis))
- changes in blood tests that check how the liver is working.

Uncommon (may affect up to 1 in 100 people):

- a state of shock resulting from blood poisoning
- serious heart problems like heart muscle degeneration (cardiomyopathy), serious changes in your heart's rhythm even with fainting heart attack
- increased blood pressure
- blood clot (thrombosis), inflammation of a vein in connection with blood clots.
- yellowing of the skin (jaundice).

Rare (may affect up to 1 in 1,000 people):

- pneumonia
- reduced number of a type of white blood cell with fever (febrile neutropenia)
- serious allergic (anaphylactic) reaction. Effects on the nerves, which can cause muscle weakness in the arms and legs
- difficulty in breathing, fluid on the lungs, inflammation of the lungs and other lung problems (lung fibrosis, pulmonary embolism), markedly impaired pulmonary function (respiratory failure)
- itching, rash and reddened skin
- weakness, high temperature (fever), dehydration, oedema, feeling ill
- blood poisoning
- blockage of the intestines, penetration of the wall of the small intestine or large bowel, inflammation of the lining of the belly (peritoneum), inflammation of the intestine caused by inadequate blood supply, inflammation of the pancreas
- increased level of the substance creatinine in the blood.
- Heart problems which can cause shortness of breath or ankle swelling

Very rare (may affect up to 1 in 10,000 people):

- acute leukaemia (a type of blood cancer), myelodysplastic syndrome (a diverse collection of blood cell disorders)
- life threatening allergic reaction (anaphylactic shock)
- loss of appetite, shock due to decreased blood pressure, cough
- effects on the nervous system which can cause paralysis of the intestines (gut) and a decreasein blood pressure when standing up or sitting up from a lying down position
- fits (epileptic seizures), cramps, confusion, dizziness, alteration in brain function or structure, headache, loss of the ability to coordinate muscular movement
- problems with eyesight and visual disturbances, usually in patients given larger doses
- reduction or loss of hearing, ringing in the ears (tinnitus), vertigo
- abnormal heart rhythm (atrial fibrillation, supraventricular tachycardia).
- a blood clot in the mesenteric artery, pseudomembranous colitis (an infection of the colon caused by specific bacteria), inflammation of the oesophagus constipation, collection of fluid in the abdomen (belly).
- severe inflammation of the large bowel presenting with fever, watery or bloody diarrhoea, and crampy abdominal pain (neutropenic colitis)
- death of liver cells (necrosis of the liver), confusion and other effects (hepatic encephalopathy) caused by changes in the way the liver works (both with reported causes of fatal outcome)
- hives (urticaria) scaling and shedding of the skin usually accompanied by redness
- severe inflammatory eruption of the skin and mucous membranes (severity ranging from erythema multiform to Stevens-Johnson syndrome to the most serious toxic epidermal necrolysis (TEN)).
- disintegration of nails. Hands and feet should be protected against sunshine during the treatment time.

Not known (Frequency cannot be estimated):

- Hardending/thickening of the skin (sclerodema)
- a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure (this condition is called Tumour Lysis Syndrome).
- Macular oedema, photopsia, vitreous floaters
- Phlebitis
- Systemic lupus erythematosus

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom: Yellow Card Scheme at: www.mhra.gov.uk/yellowcard
Ireland:
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie
Malta: ADR Reporting at: www.medicinesauthority.gov.mt/adrportal

5. How to store Paclitaxel

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Store in the original package in order to protect from light.

Do not use if you notice a cloudy solution or an insoluble precipitate.

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

6. Contents of the pack and other information

What Paclitaxel contains

The active substance is paclitaxel. Each ml of concentrate for solution for infusion contains 6 mg of paclitaxel.

Each vial contains 5, 16.7 and 50 ml (equivalent to 30, 100 and 300 mg of paclitaxel respectively).

The other ingredients are citric acid anhydrous (E330), ethanol anhydrous and macrogolglycerol ricinoleate (polyoxyl castor oil) (Cremophor).

What Paclitaxel looks like and contents of the pack

Paclitaxel is a clear colourless to slightly yellow viscous solution.

Paclitaxel is packed into type 1 flint glass vials.

Pack Sizes*:*

1 x 5 ml vial (30 mg/5 ml)

1 x 20 ml vial (l00mg/16.7 ml)

1 x 50 ml vial (300 mg/50 ml)

The vials are packaged individually in a carton. Boxes containing 10 cartons are also available.

Not all presentations may be marketed.

Marketing Authorisation Holder:

Cipla (EU) Limited
Hillbrow House, Hillbrow Road,
Esher, Surrey, KT10 9NW,
United Kingdom.

Manufacturer:

Cipla (EU) Limited,

20 Balderton Street, London W1K 6TL, United Kingdom

Cipla Europe NV,

Uitbreidingstraat 80, 2600 Antwerp, Belgium

This medicinal product is authorised in the Member States of the EEA under the following names:

Member State	Product Name
United Kingdom	Paclitaxel 6 mg/ml concentrate for solution for infusion
Ireland	Paclitaxel 6 mg/ml concentrate for solution for infusion
Malta	Paclitaxel 6 mg/ml concentrate for solution for infusion
Italy	Paclitaxel Cipla
France	PACLITAXEL CIPLA 6 mg/ml, solution à diluer pour perfusion
Spain	Paclitaxel Cipla 6mg/ml concentrado para solución para perfusión EFG
Denmark	Paclitaxel Cipla
Sweden	Paclitaxel Cipla
Poland	Paclitaxel Cipla
Norway	Paclitaxel Cipla
Germany	Paclitaxel Cipla 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung

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INFORMATION FOR HEALTH PROFESSIONALS

Below is a summary of information to assist in the administration of Paclitaxel. You should be experienced in the handling and use of cytotoxic agents and be familiar with the SmPC for Paclitaxel.

Reference should be made to guidelines on the safe handling of antineoplastic agents.

Handling: as with all antineoplastic agents, caution should be exercised when handling Paclitaxel Concentrate for solution for infusion. 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.

Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25 °C. Other in-use storage times and conditions are the responsibility of the user.

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.
Preparation, storage and administration should be carried out in non-PVC containing equipment.

Preparation for IV administration: prior to infusion, Paclitaxel 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, or 5 % Dextrose in Ringer's Injection, to a final concentration of 0.3 to 1.2 mg/ml.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2 °C to 8 °C and at 25 °C for 7 days when diluted in 5 % Dextrose Injection, 5 % Dextrose and 0.9 % Sodium chloride Injection, 5 % Dextrose in Ringer's Injection and for 14 days when diluted in 0.9 % Sodium chloride Injection.

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. After dilution the solution is for single use only.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel should be administered through an in line filter with a microporous membrane ≤ 0.22 μm. No significant losses in potency have been noted following simulated delivery of

the solution through IV tubing containing an in line filter.

There have been rare reports of precipitation during Paclitaxel infusions, usually towards the end of a 24hr 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 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.

Pregnant women or women who may become pregnant, should not handle this product.

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.

Administration and dosage
All patients should be premedicated with corticosteroids, antihistamines and H_2 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 ≤ 0.22 μm.

The recommended doses for the intravenous infusion of PACLITAXEL are as follows:

- First-line ovarian cancer:

  135 mg/m^2 over 24 hours, followed by cisplatin 75 mg/m^2; or

  175 mg/m^2 over 3 hours followed by cisplatin 75 mg/m^2;

- Second-line ovarian or breast cancer:

  175 mg/m^2 over 3 hours;

- Adjuvant breast cancer:

  175 mg/m^2 over 3 hours; following anthracycline and cyclophosphamide (AC) therapy;

- First-line breast cancer:

  220 mg/m^2 over 3 hours, 24 hours after doxorubicin (50 mg/m^2),

  175 mg/m^2 over 3 hours, after trastuzumab (see trastuzumab SPC);

- Non-small cell lung cancer:

  175 mg/m^2 over 3 hours followed by cisplatin 80 mg/m^2;

- AIDs related Kaposi's sarcoma:

  100 mg/m^2 over 3 hours.

There should be a 3-week interval between courses, dependent upon patient tolerance.

PACLITAXEL should not be readministered until the neutrophil count is $\geq 1.5x10^9$/L and the platelet count is $\geq 100x10^9$/L. Patients experiencing severe neutropenia or severe peripheral neuropathy should be subject to a dose reduction of 20 % for subsequent courses.

Storage
After opening before dilution the vials should not be stored above 25 °C and should be stored in the original package to protect from light. If refrigerated, a precipitate may form which redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy, or an insoluble precipitate is noted, the vial should be discarded. Freezing does not adversely affect the product.