

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
2. What you need to know before you use **Paclitaxel**
3. How to use **Paclitaxel**
4. Possible side effects
5. How to store **Paclitaxel**
6. Contents of the pack and other information

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 spread 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 (Acquired Immuno-Deficiency Syndrome)-related Kaposi's sarcoma (KS):

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

2. What you need to know before you use Paclitaxel

You may need to have laboratory tests (eg blood tests) to ensure that you can be given this medicinal product. Some patients may also need to have heart tests.

Do not use Paclitaxel

- if you are allergic (hypersensitive) to paclitaxel or any other ingredients of this medicine (listed in section 6), especially macroglycerol ricinoleate (polyoxyl castor oil).
- if you are breast-feeding.
- if you have too few white blood cells count (baseline neutrophil counts $<1.5 \times 10^9/l$ - your doctor will advise you on this) or platelets $< 100 \times 10^9/l$ ($<75 \times 10^9/l$ for KS patients) 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 you have severe liver problems.

If any of these apply to you, talk to your doctor or pharmacist before starting treatment with Paclitaxel.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using 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 (pseudomembranous 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).
- if your blood cell counts are abnormal.

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

Speak to your doctor when taking paclitaxel at the same time as any of the following:

- medicines for treating infection (i.e. antibiotics such as erythromycin, rifampicin, etc.; ask your doctor, nurse or pharmacist if you are unsure whether the medicine you are taking is an antibiotic), and including medicines for treating fungal infections (e.g. ketoconazole)
- medicines used to help you stabilize your mood also sometimes referred to as anti-depressants (e.g. fluoxetine)
- medicines used to treat seizures (epilepsy) (e.g. carbamazepine, phenytoin)
- medicines used to help you lower blood lipid levels (e.g. gemfibrozil)
- medicines used for heartburn or stomach ulcers (e.g. cimetidine)
- medicines used to treat HIV and AIDS (e.g. ritonavir, zidovudine, zalcitabine, didanosine, efavirenz, nevirapine)
- a medicine called clopidogrel used to prevent blood clots.
- cisplatin (to treat cancer): Paclitaxel must be given before cisplatin. Your kidney 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 doxorubicin in your body.

Paclitaxel with food, drink and alcohol

Paclitaxel is unaffected by food and drink.

Pregnancy, breast-feeding and fertility

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 must not be given if you are pregnant unless clearly advised. This medicine may cause birth defects, therefore, you must not become pregnant during treatment with paclitaxel and you and/or your partners must use an effective method of contraception whilst you are receiving treatment with paclitaxel and for 6 months after treatment has finished. If pregnancy occurs during treatment, or within the six months after treatment has finished, inform your doctor immediately.

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.

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.

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, nausea or tiredness.

Paclitaxel contains macroglycerol ricinolate (polyoxyl castor oil) and ethanol

This medicinal product contains macroglycerol ricinolate (polyoxyl castor oil) which 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.

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).

Your treatment will usually be given to you in hospital. Paclitaxel will normally be given to you by a doctor or a nurse through a drip (infusion) into a vein. Paclitaxel may be given alone or in combination with other anti-cancer medicines. 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 175mg/m², 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 175mg/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/m². The timing of paclitaxel administration after trastuzumab will depend on how you react to this medicine.

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.

If you are given more Paclitaxel than you should

Your dose will be carefully calculated by the doctors, so overdose is unlikely. However, if too 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.

If you experience any of the following side effects, tell your doctor immediately as these are all serious. You may need urgent medical attention or hospitalisation:

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

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

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

- 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

Other known side effects are

Tell your doctor as soon as possible if you notice any of the following.

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

- 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.
- infection – usually of the urinary tract and upper respiratory tract. This may be associated with low blood cell count resulting from receiving paclitaxel. This can sometimes be fatal
- mild allergic reactions including flushing and skin rash
- nerve problems affecting the hands and or feet (peripheral neuropathy)*, which can cause tingling feelings in the skin, numbness and/or pain
* Can persist beyond 6 months of paclitaxel discontinuation
- low blood pressure which may cause you to feel light-headed, particularly when standing up
- feeling sick (nausea), being sick (vomiting) and diarrhoea
- loss of hair (the majority of cases of hair loss happened less than one month after starting paclitaxel. When it happens, hair loss is pronounced (over 50%) in the majority of patients).
- muscle or joint pain
- 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
- soreness of the mouth or tongue.

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

- slow heart beat (pulse)
- temporary mild changes to the nail and skin
- 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)
- changes in blood tests that show how your liver is working.

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

- irregular heartbeats
- fainting
- serious heart problems like heart muscle degeneration (cardiomyopathy), serious changes in your heart's rhythm sometimes with fainting heart attack
- increased blood pressure (may give you headaches)
- pain in the middle of the your chest which may be caused by heart disease
- irregular heartbeat (may be caused by irregular impulse conduction)
- increased level of bilirubin in your blood, which could cause yellowing of the skin and the whites of the eyes (jaundice).

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

- pneumonia
- effect on nerves that control the muscles, resulting in muscle weakness in arms and legs (motor neuropathy)
- reduced number of a type of white blood cell with fever (febrile neutropenia)
- problems with your lungs such as inflammation or accumulation of fluids, which may make it difficult to breathe
- itching, rash and reddened skin
- weakness, high temperature (fever), dehydration, accumulation of fluid in the whole body (oedema), feeling ill
- Abdominal pain caused by inflammation in your bowel, bowel obstruction or perforation of the wall of your bowel, 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)
- loss of appetite, shock due to decreased blood pressure, 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
- confusion,
- dizziness,
- 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.
- headache,
- problems with eyesight and visual disturbances, usually in patients given larger doses
- reduction or loss of hearing, ringing in the ears (tinnitus)
- 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 and 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
- effect on the brain (encephalopathy)
- balance problems
- staggering when walking
- 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.

Not known (frequency cannot be estimated from the available data):

- hardening/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).
- a swelling of part of the back of your eye (macular oedema),
- visual disturbances such as seeing flashes of light (photopsia) or floaters
- inflammation of the veins (phlebitis)
- an autoimmune disorder that may affect your skin, joints, kidneys, brain, and other organs (systemic lupus erythematosus)
- a whistling sound when you breathe (wheezing)
- disseminated intravascular coagulation, or “DIC” has been reported. This concerns a serious condition that makes people bleed too easily, get blood clots too easily, or both.
- redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel

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.

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).

Ireland:

HPRA Pharmacovigilance

Website: www.hpra.ie

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

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 (30mg/5ml)

1 x 20 ml vial (100mg/16.7ml)

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

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 Europe NV

De Keyserlei 58-60, Box-19, 2018 Antwerp, Belgium.

Manufacturer:

Cipla (EU) Limited,

4th Floor, 1 Kingdom Street, London, W2 6BY, United Kingdom

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
France	PACLITAXEL CIPLA 6 mg/ml, solution à diluer pour perfusion
Germany	Paclitaxel Cipla 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung

This leaflet was last revised in 12/2019.

✂----- 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: Paclitaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling Paclitaxel Concentrate for solution for infusion. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. 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. However haziness does not affect the potency of the product. The solution of infusion should be administered through an in line filter with microporous membrane ≤ 0.22 microns. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in line (0.22 micron) filter.

There have been some reports of precipitation during Paclitaxel infusions, with precipitation usually taking place 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 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, infusion or otherwise coming into contact with paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

Administration and dosage

Pre-medication: All patients must be given pre-medication consisting of corticosteroids, antihistamines and H₂-receptor antagonists prior to paclitaxel administration. The diluted PACLITAXEL infusion should be administered using non-PVC containing equipment through an in-line filter with a microporous membrane ≤ 0.22 microns.

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

- First-line ovarian cancer:
135 mg/m² over 24 hours, followed by cisplatin 75 mg/m²; or
175 mg/m² over 3 hours followed by cisplatin 75 mg/m²;
- Second-line ovarian or breast cancer:
175 mg/m² over 3 hours;
- Adjuvant breast cancer:
175 mg/m² over 3 hours; following anthracycline and cyclophosphamide (AC) therapy;

- First-line breast cancer:
220 mg/m² over 3 hours, 24 hours after doxorubicin (50 mg/m²),
175 mg/m² over 3 hours, after trastuzumab (see trastuzumab SPC);
- Non-small cell lung cancer:
175 mg/m² over 3 hours followed by cisplatin 80 mg/m²;
- AIDs related Kaposi's sarcoma:
100 mg/m² over 3 hours.

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

Paclitaxel should not be re-administered until the neutrophil count is $\geq 1.5 \times 10^9/\text{L}$ and the platelet count is $\geq 100 \times 10^9/\text{L}$. 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.