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.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

Paclitaxel concentrate for solution for infusion is given only by a doctor or nurse. They can answer any questions you may have after reading this package leaflet.

1. What Paclitaxel is and what it is used for

This medicinal product is used for treatment of cancer. It can be cancer in the ovaries or breast cancer (advanced or spreading ovarian cancer, advanced or spreading breast cancer). This medicinal product may also be used for a special cancer in the lungs (advanced non-small-cell lung cancer, NSCLC) in patients who cannot be treated with surgery and/or radiotherapy. Paclitaxel may also be used for a special cancer, called Kaposi´s sarcoma, which may be associated with AIDS (Acquired Immuno-Deficiency Syndrome) caused by an HIV disease) where other treatments i.e. liposomal anthracyclines have not worked. Paclitaxel works by stopping cell division and is used to prevent the growth of cancer cells.

2. What you need to know before you use Paclitaxel

Do not use Paclitaxel
- if you are allergic to paclitaxel or any of the other ingredients of this medicine (listed in section 6). One of the ingredients, macrogolglycerol ricinoleate, can cause severe allergic reactions
- if you are breast-feeding
- if the number of white blood cells (neutrophils) is too low. This is measured by a doctor or nurse.
- In patients with Kaposi's sarcoma, this product should not be used if you have a serious uncontrolled infection.

If you are unsure about anything, ask your doctor or pharmacist.

Warning and precautions
Talk to your doctor before using Paclitaxel
- if you have heart disease or liver problems
- when diarrhoea occurs during or shortly after treatment with paclitaxel (pseudomembranous colitis)
- if you have Kaposi's sarcoma and severe inflammation of the mucous membrane (membranes lining the passages of the body that open to the outside) occurs

- if you have had nerve problems in your hands or in feet, such as numbness, tingling or burning (peripheral neuropathy)
- if you have blood problems, such as changes in the number of some cells
- if Paclitaxel is given to you in combination with radiotherapy of the lung.

Children and adolescents
This medicine should not be given to children and adolescents under 18 years of age.

Other medicines and Paclitaxel
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

When used in combination, Paclitaxel should be given before cisplatin. Paclitaxel should be given 24 hours after doxorubicin.

Speak to your doctor when taking paclitaxel at the same time as any of the following:
- medicines for treating infections (i.e. antibiotics such 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, phenobarbital)
- medicines used to help you lower blood lipid levels (e.g. gemfibrozil)
- medicine used for heartburn or stomach ulcers (e.g. cimetidine)
- medicines used to treat HIV and AIDS (e.g. ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, nevirapine)
- a medicine called clopidogrel used to prevent blood clots.

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.

Pregnancy
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 must use an effective method of contraception whilst you are receiving treatment and for six months after treatment with paclitaxel is completed. If pregnancy occurs during treatment, or within the six months after treatment has finished, inform your doctor immediately.

Breast-feeding
Paclitaxel should not be used when you are breast-feeding. You should stop breast feeding while you are being treated with Paclitaxel. Do not restart breast feeding until your doctor tells you it is safe to do so.

Fertility
This medicine may cause sterility, which could be permanent. Male patients should seek advice regarding cryoconservation of sperm prior to treatment.

Both females and males of fertile age, and/or their partners should use contraceptives for at least 6 months after treatment with Paclitaxel.

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 alcohol and magrogolglycerol ricinoleate
Alcohol (ethanol) approximately 50 % by volume, that is up to about 20 g per dose. This is equivalent to half a litre of beer per dose or a large glass (210 ml) of wine per dose. This amount may be dangerous for patients suffering from alcoholism and for high risk patients including those with liver problems or epilepsy (fits). The amount of alcohol in this product may alter the effects of other medicines.

Macrogolglycerol ricinoleate, which can cause severe allergic (hypersensitivity) reactions.

3. How to use Paclitaxel

Your doctor will decide how much Paclitaxel you will be given. It is given under the supervision of a doctor, who can give you more information. The dose will depend on the type and the extent of the cancer, and your body surface in square metres (m^2) which is calculated from your height and weight. The dose you receive will also depend on results of your blood tests.

Paclitaxel solution has to be diluted before being given to you.

Paclitaxel is given by infusion (a drip) into a vein for 3 or 24 hours. Treatment is usually repeated every three weeks. Treatment of AIDS-related Kaposi's sarcoma is repeated every other week.

Depending on the type and severity of the cancer you will receive Paclitaxel either alone or in combination with another anticancer agent.

Each time before you are given Paclitaxel, you will be given other medicines (premedication) such as dexamethasone, diphenhydramine and cimetidine, or ranitidine. This is necessary to decrease the risk of severe allergic (hypersensitive) reactions (see section 4. Possible side effects, uncommon).

Use in children and adolescents
This medicine should not be given to children and adolescents under 18 years old.

If you are given too much Paclitaxel
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.
The following side effects may occur after treatment with Paclitaxel infusion.

The most frequent side effects are hair loss and decreased blood cell count. Your hair grows back and your blood cell count returns to normal after you have finished your paclitaxel treatment.

<u>If any of the following happens, tell your doctor immediately:</u>
- Any abnormal bruising, bleeding, or signs of infections such as a sore throat and high temperature.
- Severe allergic 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.

- Breathlessness and dry cough due to damage to the lung.
- Reaction at the injection site, e.g. local swelling, pain, redness

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).
- Decreased number of blood platelets 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.
- Muscle or joint pain.
- Inflammation of areas such as the lining of the mouth.
- Loss of hair (the majority of cases of hair loss happened less than one month after starting paclitaxel treatment. When it happens, hair loss is pronounced (over 50%) in the majority of patients)

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 allergic (hypersensitivity) reactions with e.g. decreased or increased blood pressure, swelling of the face, difficulty in breathing, skin rash, chills, back pain, chest pain, fast heart beat, abdominal pain, pain in arms and legs, sweating.
- 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)
- Heart failure
- 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

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 decrease in 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 cases 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 multiforme 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 from the available data):
- Tumour lysis syndrome (complications which are caused by the break-down products of dying cancer cells) this may cause for example muscle weakness due to increased levels of potassium in your blood, acute kidney failure due to increased levels of phosphate in you blood, seizures and movement disorders due to lower levels of calcium in your blood.
- Eye complications (macular oedema, flashes of light, seeing spots)
- Vein inflammation
- Hard skin (scleroderma)
- Systemic lupus erythematosus, mainly characterized by recurrent red patches on the skin usually accompanied by episodes of inflammation of joints, tendons and other connective tissues and organs.
- 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.
-

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. 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, email: medsafety@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.

Keep the vial in the outer carton in order to protect from light.

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

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

What Paclitaxel contains

- The active substance is paclitaxel.
- 1 ml of concentrate for solution for infusion contains 6 mg paclitaxel.
- The other ingredients are citric acid, anhydrous, macrogolglycerol ricinoleate and ethanol, anhydrous.

What Paclitaxel looks like and contents of the pack

Paclitaxel 6 mg/ml concentrate for solution for infusion is a clear, colourless to pale yellow, slightly viscous solution and is packed into glass vials.

Pack sizes:
1 x 5 ml vial (30 mg/5 ml)
1 x 16,7 ml vial (100 mg/16,7 ml)
1 x 25 ml vial (150 mg/25 ml)
1 x 50 ml vial (300 mg/50 ml)

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

Manufacturer
S.C. Sindan- Pharma S.R.L
11 Ion Mihalache Blvd
011171 Bucharest
Romania

or

Actavis Italy S.p.A. – Nerviano Plant
Viale Pasteur 10
20014 Nerviano (MI)
Italy

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

United Kingdom	Paclitaxel 6mg/ml concentrate for solution for infusion
Ireland	Paclitaxel 6mg/ml concentrate for solution for infusion

This leaflet was last revised in February 2018

Detailed information on this medicine is available on the web site of {MA/Agency}

The following information is intended for healthcare professionals only:

Instructions for use

CYTOSTATIC AGENT

Handling of Paclitaxel
As with all cytostatic agents, caution should be exercised when handling Paclitaxel. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Precautions should be taken to avoid contact with the skin and mucous membranes. Following topical exposure, tingling, burning and erythema have been observed. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

Protection instructions for preparation of Paclitaxel solution for infusion

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Opened containers, like injection vials and infusion bottles and used canules, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
3. Follow the instructions below in case of spillage:
   - protective clothing should be worn
   - broken glass should be collected and placed in the container for HAZARDOUS WASTE
   - contaminated surfaces should be flushed properly with copious amounts of cold water
   - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
4. In the event of Paclitaxel contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
5. In case of contact of Paclitaxel with eyes, wash them thouroughly with plenty of cold water. Contact an ophthalmologist immediately.

Preparation of infusion solution
So called "closed system", e.g. the Chemo-Dispensing Pin device or similar devices, should not be used for withdrawal of the doses from injection vial 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 (see section "Incompatibilities" below).

Prior to infusion, Paclitaxel 6 mg/ml concentrate for solution for infusion must be diluted, using aseptic techniques. The following solutions for infusion can be used for dilution: 0.9 % Sodium Chloride solution

for infusion, or 5 % Glucose solution for infusion, or 5 % Glucose and 0.9 % Sodium Chloride solution for infusion, or 5 % Glucose in Ringer's solution for infusion, to a final concentration of 0.3 to 1.2 mg/ml

There have been rare reports of precipitation during paclitaxel 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 should be used as soon as possible after dilution and excessive agitation, vibration or shaking should be avoided.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. In order to reduce the precipitation risk the diluted Paclitaxel infusion should be used as soon as possible after dilution.

Infusion technique
Paclitaxel infusion solution should be administered as intravenous infusion for 3 or 24 hours.

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.)

The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regurlarly inspected and the infusion should be stopped if precipitation is present.

Stability and storage conditions
Store the vial in 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. An expiry date is given on the outer carton and vial label of the product. It should not be used after this date.

After opening: From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 7 days when diluted in a 5 % glucose solution and 5 % glucose in Ringer solution for injection and for 14 days when diluted in sodium chloride 0.9 %. 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 usually should not be more than 24 hours at 2-8 ºC, unless the dilution is performed in controlled and validated aseptic conditions.
After the dilution, the solution is for single use.

Incompatibilities
To minimise patient exposure to plasticizer DEHP (di-2-ethylhexyl phtalate), which may be leached from plasticised PVC infusion bags, sets, or other medical intruments, diluted paclitaxel solutions should be stored in non-PVC bottles (glass, polypropene) or plastic bags (polypropene, polyolefin) and administered through polyethene-lined administration sets. Use of filter devices (eg. IVEX-2) which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

This medicinal product must not be mixed with other medicinal products except thos mentioned above in section "Preparation of infusion solution".

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.