Patient Information Leaflet

Paclitaxel 6mg/ml Concentrate For Solution For Infusion

(Paclitaxel)

Read all of this leaflet carefully before you are given this medicine.
- **Keep this leaflet. You may need to read it again.**
- **If you have any further questions, ask your doctor.**
- **If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.**

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 packaging leaflet.

1. WHAT PACLITAXEL IS AND WHAT IT IS USED FOR

This medicinal product is used for treatment of cancer. It can be cancer of 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) 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. BEFORE YOU ARE GIVEN PACLITAXEL

You should not be given paclitaxel:
- if you are allergic (hypersensitive) to paclitaxel or any of the other ingredients. One of the ingredients, macrogolglycerol ricinoleate, can cause severe allergic reactions
- if you are pregnant or breast feeding
- if the number of white blood cells (neutrophils) is too low. This is measured by a doctor or nurse
- if you have Kaposi's sarcoma and you have a serious uncontrolled infection.

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

Your doctor will take special care when giving you paclitaxel:
- if you have heart disease or liver problems
- if 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 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

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Pregnacy and Breast-feeding
Pregnancy
Do not use paclitaxel if you think you are pregnant or you are trying to become pregnant.
Paclitaxel can damage the unborn baby.

Pregnancy must be avoided and **both partners should use reliable contraception during treatment with paclitaxel and for at least six months after treatment.**

Tell your doctor immediately if you do become pregnant.

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 the doctor tells you it is safe to do so. Ask you doctor or pharmacist for advice before taking any medicine.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you have obtained without a prescription.

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

Special care should be observed if you are taking medicines which influence the metabolism of paclitaxel such as: erythromycin, fluoxetine, gemfibrozil, rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, and nevirapine and for HIV patients receiving protease inhibitors (ritonavir, nelfinavir) as concomitant therapy.

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.

Important information about some of the ingredients of paclitaxel

Paclitaxel contains:

• Alcohol (ethanol) approximately 50% by volume, that is up to about 20g per dose. This is equivalent to half a litre of beer per dose or a large glass (210ml) 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 PACLITAXEL IS GIVEN TO YOU

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 hours. Treatment is usually repeated every three weeks. Treatments 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).

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 hands, legs or feet, and stomach upsets including vomiting and diarrhoea.

4. POSSIBLE SIDE EFFECTS

Like all medicines, paclitaxel can cause side effects, although not everybody gets them. The following side effects may occur after treatment with paclitaxel infusion.

The most common 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 infection 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 (affects more than 1 out of 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.
  * Can persist beyond 6 months of paclitaxel discontinuation

- 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 (affects more than 1 out of 100 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 (affects less than 1 out of 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 to 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 (affects less than 1 out of 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.

Very rare (occurs with less than 1 out of 10,000 of the 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 cramping abdominal pain (neutropenic colitis).
- Death of the 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

Frequency not known (cannot be estimated from the available data):
- Redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report any 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 - Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance, Website:www.hpra.ie

5. STORING PACLITAXEL

Keep out of the sight and reach of children.

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

Do not use this medicinal product after the expiry date which is stated after "EXP". The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What paclitaxel contains:
The active substance is paclitaxel. 1ml of concentrate for solution for infusion contains 6mg paclitaxel.
The other ingredients are citric acid (anhydrous), macrogolglyerol ricinoleate, nitrogen and ethanol 96%.

What paclitaxel looks like and contents of the pack:
Paclitaxel is a clear, colourless to pale yellow, slightly viscous solution and is packed into glass vials.

Pack sizes:
1 x 5ml vial containing: 30mg paclitaxel in 5ml of solution
1 x 20ml vial containing: 100mg paclitaxel in 16.7ml of solution
1 x 50ml vial containing: 300mg paclitaxel in 16.7ml of solution
Not all pack sizes may be marketed.

Marketing Authorisation Holder for UK:
Intrapharm Laboratories Limited, The Courtyard Barns, Choke Lane, Cookham Dean, Maidenhead, Berkshire SL6 6PT, United Kingdom

Marketing authorisation holder for Ireland:
RIEMSER Pharma GmbH, An der Wiek 7, 17493 Greifswald – Insel Riems, Germany

Manufacturer:
Peckforton Pharmaceuticals Ltd, Crewe Hall, Crewe, Cheshire CW1 6UL, United Kingdom

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Tear off----------

Paclitaxel 6mg/ml Concentrate For Solution For Infusion

INFORMATION FOR HEALTH PROFESSIONALS

Handling: as with all antineoplastic agents, caution should be exercised when handling paclitaxel. Dilution should be carried out under aseptic conditions by trained personnel in a designated area

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. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

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

3. 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.

4. 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

5. Precautions should be taken to avoid contact with the skin and mucous membranes. In the event of Paclitaxel being in contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. Following topical exposure, tingling, burning and redness have been observed. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.

6. In case of contact of paclitaxel with eyes, wash them thoroughly with plenty of cold water. Contact an ophthalmologist immediately.

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

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

Preparation for IV administration: Prior to infusion, paclitaxel must be diluted, using aseptic techniques, in 0.9% sodium chloride injection, or 5% glucose injection, or 5% glucose and 0.9% sodium chloride injection, or 5% glucose in Ringer s Injection, to a final concentration of 0.3 to 1.2 mg/mL.

Solutions prepared for infusion are stable for 24 hours at 25°C. Following multiple needle entries and product withdrawals, paclitaxel infusion multidose 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. Diluted solutions should not be refrigerated.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel infusion should be administered through an in-line filter with a microporous membrane ≤0.22μm. 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 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 inspected regularly and the infusion should be stopped if precipitation is present.

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

Diluted solution should be for single use only.

Dosage and Method of Administration:

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel infusion.

Ovarian carcinoma

First-line chemotherapy of ovarian carcinoma: although other dosage regimens are under investigation, a combination regimen of paclitaxel infusion and cisplatin is recommended. According to duration of infusion, two doses of paclitaxel infusion are recommended: paclitaxel infusion 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin at a dose of 75 mg/m^2 every three weeks or paclitaxel infusion 135 mg/m^2, in a 24-hour infusion, followed by cisplatin 75 mg/m^2, with a three week interval between courses.

Second-line chemotherapy of ovarian carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, with a three week interval between courses.

Breast carcinoma

Adjuvant chemotherapy in breast carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours every three weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma: when used in combination with doxorubicin (50 mg/m^2), paclitaxel infusion should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel infusion is 220 mg/m^2 administered intravenously over a period of three hours, with a three-week interval between courses.

When used in combination with trastuzumab, the recommended dose of paclitaxel infusion is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated (for detailed trastuzumab posology see the Summary of Product Characteristics of trastuzumab).

Second-line chemotherapy of breast carcinoma: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, with a three-week interval between courses.

Advanced non-small cell lung carcinoma

Treatment of advanced NSCLC: the recommended dose of paclitaxel infusion is 175 mg/m^2 administered over a period of three hours, followed by cisplatin 80 mg/m^2, with a three week interval between courses.

AIDS-related Kaposi's sarcoma

Treatment of AIDS-related KS: the recommended dose of paclitaxel infusion is 100 mg/m^2 administered as a three-hour intravenous infusion every two weeks. Subsequent doses of paclitaxel infusion should be administered according to individual patient tolerance.

Paclitaxel infusion should not be readministered until the neutrophil count is ≥1,500/mm^3 (≥1,000/mm^3 for KS patients) and the platelet count is ≥100,000/mm^3 (≥75,000/mm^3 for KS patients). Patients who experience severe neutropenia (neutrophil count < 500/mm^3 for ≥7 days) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for KS patients).

Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment should not be treated with paclitaxel.

Paediatric use: Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Storage and Disposal

Do not store unopened vials above 25°C and keep in the outer carton to protect from light.

Disposal: All items used for preparation, administration or otherwise coming into contact with paclitaxel injection should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

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