

Package leaflet: Information for the user

Paclitaxel 6 mg/ml concentrate for solution for infusion Paclitaxel

Read all of these 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 nurse
- If you get any side effects talk to your doctor 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 Paclitaxel is given to you
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 the leaflet it will be called "Paclitaxel".

Paclitaxel 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-line 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-line therapy for advanced disease or disease which has spread to other parts of the body (metastatic disease). Paclitaxel is either combined with an *anthracycline* (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 HER 2, see package leaflet of trastuzumab).
- as an additional treatment with anthracycline and cyclophosphamide (AC).
- as a 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 another treatment (i.e. liposomal anthracyclines) has been tried but did not work.

2. What you need to know before you use Paclitaxel

You should not be given Paclitaxel

- if you are allergic to paclitaxel or any of the other ingredients of this medicine (listed in section 6) especially polyoxyethylated castor oil (macrogolglycerol ricinoleate);
- if you are breast-feeding;

- if you have too few white blood cells count in your blood (baseline neutrophil counts $<1.5 \times 10^9/l$ or $<1.0 \times 10^9/l$ for Kaposi's sarcoma patients - your doctor will advise you on this). Your doctor will take blood samples to check this.
- if you have serious and uncontrolled infections (only in case Paclitaxel is used to treat Kaposi's sarcoma).

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

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

Warnings and precautions

Talk to your doctor before using Paclitaxel

To minimize allergic reactions, you will be given other medicines before you receive Paclitaxel.

- 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 you have numbness, tingling, pricking sensations, sensitivity to touch, or weakness of the arms and legs (signs of peripheral neuropathy); a dose reduction of Paclitaxel may be necessary
- if you have severe liver problems; in that case the use of Paclitaxel is not recommended.
- if you have heart conduction problems.
- 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 had previous radiation to your chest (because it may increase the risk of lung inflammation).
- if you have a sore or red mouth (signs of mucositis) and are treated for Kaposi's Sarcoma. You may need a lower dose.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Tell your doctor immediately if any of these apply to you.

Paclitaxel should always be administered into veins. Administration of Paclitaxel in the arteries can cause inflammation of the arteries, and you can suffer from pain, swelling, redness and heat.

Other medicines and Paclitaxel

Tell your doctor if you are taking or have recently taken or might take any other medicines.

Interaction means that different medicines may influence each other. Speak to your doctor when taking paclitaxel at the same time as any of the following:

- 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.
- 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 antidepressants (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).
- 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

Pregnancy

Tell your doctor if you are pregnant or think you may be pregnant before receiving treatment with Paclitaxel. 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.

Fertility

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.

Breast-feeding

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 due to possible effects on your central nervous system. As in all cases, you should not drive or use machines if you feel dizzy or light-headed.

Paclitaxel contains castor oil that may cause severe allergic reactions. If you are allergic to castor oil, talk to your doctor before you receive Paclitaxel.

Paclitaxel contains alcohol – each millilitre of Paclitaxel includes 0.396 g of alcohol. A Paclitaxel dose of 300 mg/50 ml contains 20 g of alcohol, equivalent to 434 ml beer or 181 ml wine.

Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines.

3. How Paclitaxel is given to you

- **To minimise allergic reactions**, you will be given other medicines before you receive Paclitaxel. These medicines can be given as either tablets or infusion into a vein or both.
- **You will receive Paclitaxel as a drip** into one of your veins (by intravenous infusion), through an in-line filter. Paclitaxel will be administered to you by a healthcare professional. He or she will prepare the solution for infusion before it is given to you. The dose you receive will also depend on results of your blood tests. Depending on the type and severity of the cancer you will receive Paclitaxel either alone or in combination with another anticancer agent.
- Paclitaxel should always be administered into one of your veins over a period of 3 or 24 hours. It is usually given every 2 or 3 weeks, unless your doctor decides otherwise. Your doctor will inform you about the number of courses of Paclitaxel you need to receive.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

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 **fever, severe chills, sore throat or mouth ulcers** (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.

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

- Minor allergic reactions such as flushing, rash, itching
- Infections: mainly upper respiratory infection, urinary tract infection
- Sore throat or mouth ulcers, sore and red mouth, diarrhoea, feeling or being sick (nausea, vomiting)
- Hair loss (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).
- Pain in the muscles, pain in the joints
- Numbness, tingling or weakness in arms and legs (all symptoms of peripheral neuropathy)
- Tests may show: reduction of blood platelet count which can lead to bleeding and bruising more easily than normal, white or red blood cells count, low blood pressure

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

- Temporary mild nail change and skin changes, reactions at injection sites (localised swelling, pain, and redness of the skin)
- Tests may show: slower heart rate, severe elevation in liver enzymes (alkaline phosphatase and AST - SGOT)

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

- Shock due to infections (known as 'septic shock')
- Palpitations, cardiac dysfunction (AV block, cardiomyopathy), rapid beating of the heart, heart attack
- Significant allergic reactions (sweating, fainting, syncope), **respiratory distress**, swelling of the face, lips, mouth, tongue or throat, back pain, chest pain, pain around hands and feet, chills, abdominal (tummy) pain)
- Phlebitis (inflammation of a vein)
- Tests may show: severe elevation of bilirubin (jaundice), high blood pressure, and blood clot.

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

- Shortage of white blood cells with fever and increased risk of infection (febrile neutropenia)
- Affection of nerves with feeling of weakness in muscles of arms and legs (motor neuropathy)
- Shortness of breath, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion
- Bowel obstruction, bowel perforation, inflammation of colon (ischaemic colitis), inflammation of the pancreas (pancreatitis)
- Pruritus, rash, skin redness (erythema)
- Blood poisoning (sepsis), peritonitis, pneumonia
- Pyrexia, dehydration, asthenia, oedema, malaise
- Serious and potentially fatal hypersensitivity reactions (anaphylactic reactions)
- Tests may show: increase in blood creatinine indicating renal function impairment
- Heart failure

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

- Irregular rapid heart rhythm (atrial fibrillation, supraventricular tachycardia)
- Sudden disorder in blood forming cells (acute myeloid leukaemia, myelodysplastic syndrome)
- Optic nerve and/or visual disturbances (scintillating scotomata)
- Hearing loss or reduction (ototoxicity), ringing in the ears (tinnitus), vertigo
- Cough
- Blood clot in a blood vessel of abdomen and bowel (mesenteric thrombosis), inflammation of colon sometimes with persistent severe diarrhoea (pseudomembranous colitis, neutropenic colitis), dropsy (ascites), oesophagitis,

constipation.

- Serious hypersensitivity reactions including fever, skin redness, pain in joints and/or inflammation of the eye (Stevens-Johnson syndrome), local peeling of the skin (epidermal necrolysis), redness with irregular red (exudative) spots (erythema multiforme), inflammation of the skin with blisters and peeling (exfoliative dermatitis), urticaria, loose nails (patients on therapy should wear sun protection on hands and feet).
- Loss of appetite (anorexia).
- Serious and potentially fatal hypersensitivity reactions with shock (anaphylactic shock).
- Disturbed liver function (hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome))
- Confusional state.
- Grand mal seizures, brain nerve disorder (autonomic neuropathy; affection of the involuntary body functions, this can result in ileus and low blood pressure), convulsions, brain disease (encephalopathy), dizziness, headache, problems with coordination (ataxia)

Not known (*cannot be estimated from the available data*)

- Rapid destruction of tumors (tumor lysis syndrome)
- Fluid collection in the macula of the eye (macular oedema), presence of perceived flashes of light in the eye (photopsia), deposits within the eye's vitreous humour (vitreous floaters)
- Inflammation of the veins (phlebitis)
- Thickening and hardening of the skin as well as the blood vessels and the internal organs (scleroderma)
- "Butterfly rash" (systemic lupus erythematosus)
- 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.

If you get any side effects talk to your doctor. This includes any side effects not listed in this leaflet. You can also report side effects directly to Pharmacovigilance Section, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.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 carton after EXP. The expiry date refers to the last day of that month.

Before opening

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

Freezing does not adversely affect the product.

After opening before dilution (description of the conditions)

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.

After dilution (description of the conditions)

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, store in a refrigerator (2 to 8°C) for no more than 24 hours, unless dilution has taken place in controlled and validated aseptic conditions. For more details on the stability after dilution, see the section for health-care professionals.

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

Do not throw away 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. Content 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 or 50 ml (equivalent to 30, 100 or 300 mg of paclitaxel respectively).

The other ingredients are polyoxylethylated castor oil (macrogolglycerol ricinoleate) and ethanol.

What Paclitaxel looks like and contents of the pack

Paclitaxel is a clear colourless to slightly yellow solution.

It is available in vials containing 5 ml, 16.7 ml or 50 ml of concentrate for solution for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Stragen Nordic A/S
Helsingørsgade 8C
3400 Hillerød
Denmark
Telefon: +45 48 10 88 10
Email: info@stragen.dk

Manufacturer

Corden Pharma Latina S.p.A.
Via del Murillo Km 2.800
04013 Sermoneta
Italy

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The following information is intended for medical or healthcare professionals only

Preparation of infusion solutions:

- Containers and infusion sets used with Paclitaxel must be **DEHP-free**. This will minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may leach from PVC infusion containers or sets. Use of filter devices (e.g. IVEX-2) which incorporate short inlet and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.
- **Take care when handling Paclitaxel** as with all antineoplastic agents. Always wear adequate protective gloves when handling vials containing paclitaxel. Dilution should be performed under aseptic conditions by trained personnel in a designated area. In the event of contact with the skin, wash the area with soap and water. In the event of contact with the mucous membranes, flush thoroughly with water.
- Do not use the Chemo-Dispensing Pin device or similar devices with spikes since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Step 1: Dilute the concentrate

Before administration, **Paclitaxel** must be further diluted with either:

- 0.9% Sodium Chloride for Injection

- 5 % Dextrose for Injection
- 5% Dextrose and 0.9% Sodium Chloride for injection
- 5% Dextrose in Ringer's for Injection

The final infusion concentration of paclitaxel must range between 0.3 mg/ml and 1.2 mg/ml.

When diluted, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.

Step 2: Administer the infusion

Premedicate all patients with corticosteroids, antihistamines and H₂ antagonists prior to administration.

Do not readminister Paclitaxel until the neutrophil count is $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for Kaposi's sarcoma patients) and the platelet count is $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for Kaposi's sarcoma patients).

Avoid precipitation of the infusion solution:

- Use as soon as possible after dilution
- Avoid excessive agitation, vibration or shaking
- Flush the infusion sets thoroughly before use.
- Regularly inspect the appearance of the infusion and stop the infusion if precipitation is present.

Paclitaxel solutions prepared for infusion may be stored for up to 12 hours at 25 °C without light protection when diluted in 5% Dextrose solution or 0.9% Sodium Chloride Injection.

With light protection, chemical and physical in-use stability of the diluted solution has been demonstrated at 5° and at 25°C for 7 days when diluted in 5% Dextrose solution, and for 14 days when diluted in 0.9% Sodium Chloride Injection. From a microbiological point of view, the diluted product should be used immediately or maintained at 2 to 8°C for a maximum of 24 hours.

Paclitaxel must be administered through an appropriate in-line filter with a microporous membrane of ≤ 0.2 micrometres. DEHP-free infusion containers and administration sets must be used. Use of filter devices which incorporate short inlet and/or outlet plasticised tubing has not resulted in significant leaching of DEHP.

Step 3: Disposal

Dispose of any unused product or waste material in accordance with local requirements for handling of cytotoxic compounds.

Dose:

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

Indication	Dose	Interval between Paclitaxel courses
First-line ovarian carcinoma	135 mg/m ² over 24 hours, followed by cisplatin 75 mg/m ² <u>or</u> 175 mg/m ² over 3 hours, followed by cisplatin 75 mg/m ²	3 weeks
Second-line ovarian carcinoma	175 mg/m ² over 3 hours	3 weeks
Adjuvant breast carcinoma	175 mg/m ² over 3 hours; following anthracycline and cyclophosphamide (AC) therapy	3 weeks
First-line breast carcinoma (with doxorubicin)	220 mg/m ² over 3 hours, 24 hours after doxorubicin (50 mg/m ²)	3 weeks
First-line breast carcinoma (with trastuzumab)	175 mg/m ² over 3 hours, after trastuzumab (see trastuzumab SPC)	3 weeks
Second-line breast carcinoma	175 mg/m ² over 3 hours	3 weeks

Advanced Non-small cell lung carcinoma	175 mg/m ² over 3 hours, followed by cisplatin 80 mg/m ² ;	3 weeks
AIDS-related Kaposi's sarcoma	100 mg/m ² over 3 hours	2 weeks

Do not readminister Paclitaxel until the neutrophil count is $\geq 1,500/\text{mm}^3$ ($\geq 1,000/\text{mm}^3$ for Kaposi's sarcoma patients) and the platelet count is $\geq 100,000/\text{mm}^3$ ($\geq 75,000/\text{mm}^3$ for Kaposi's sarcoma patients).

Patients who experience severe neutropenia (neutrophil count $< 500/\text{mm}^3$ for a week or longer) or severe peripheral neuropathy should receive a dose reduction of 20% for subsequent courses (25% for Kaposi's sarcoma patients) (see Summary of Product Characteristics).

Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with Paclitaxel (see Summary of Product Characteristics).

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