PACKAGE LEAFLET

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, pharmacist or nurse.
- 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.

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 Injection".

What is in this leaflet

1. What Paclitaxel Injection is and what it is used for

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

Paclitaxel Injection 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 Injection 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).
- after initial surgery following treatment with anthracycline and cyclophosphamide (AC) as an additional treatment.
- 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 Injection

You should not be given Paclitaxel Injection
- **if you are allergic** (hypersensitive) to paclitaxel or to any of the other ingredients of this medicine (listed in section 6), especially polyoxyethylated 35 castor oil (macrogolglycerol ricinoleate 35);

- **if you are breast-feeding;**
- **if you have too few white blood cells** in your blood. Your doctor will take blood samples to check this.
- **if you have a serious and uncontrolled infection and Paclitaxel Injection is used to treat Kaposi's sarcoma.**

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

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

Warnings and precautions

Talk to your doctor or pharmacist or nurse before using Paclitaxel Injection.

To minimise allergic reactions, you will be given other medicines before you receive Paclitaxel Injection.
- 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 Injection may be necessary.
- If you have **severe liver problems**; in that case the use of Paclitaxel Injection 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 Injection. 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.

Tell your doctor immediately if any of these apply to you.
Paclitaxel Injection should always be administered into veins. Administration of Paclitaxel Injection in the arteries can cause inflammation of the arteries, and you can suffer from pain, swelling, redness and heat.

Other medicines and Paclitaxel Injection
Tell your doctor if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription. This is because Paclitaxel Injection or the other medicine may not work as well as expected, or you may be more likely to get a side effect.

Interaction means that different medicines may influence each other.

<u>Speak to your doctor when taking paclitaxel at the same time as any of the following:</u>
- medicines for treating infections (i.e. antibiotics such as erythromycin, 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, other imidazole antifungals)
- 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, saquinavir, indinavir, nelfinavir, efavirenz, nevirapine)
- a medicine called clopidogrel used to prevent blood clots.
- a medicine called rifampicin, an antibiotic used for tuberculosis. A dose increase of Paclitaxel Injection may be necessary.
- vaccines: If you have been vaccinated recently, or if you are planning to get vaccination, tell this to your doctor. The use of Paclitaxel Injection in combination with certain vaccines may lead to severe complications.
- cisplatin (to treat cancer): Paclitaxel Injection must be given before cisplatin. Your renal function may
- need to be checked more frequently.

- **doxorubicin** (to treat cancer): Paclitaxel Injection must be administered 24 hours after doxorubicin, to
- avoid high level of doxorubicin in your body.

Paclitaxel Injection with food, drink and alcohol
Paclitaxel Injection 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.

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

Male patients treated with paclitaxel are advised not to father a child during and up to six months after treatment.

If you are breast-feeding, tell your doctor. Stop breast-feeding if you are taking Paclitaxel Injection. 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
Paclitaxel Injection may cause side effects such as tiredness (very common) and dizziness (common) that may affect your ability to drive and use machinery. If you experience these symptoms, do not drive or operate machinery until they have fully resolved. If you are given other medicines as part of your treatment, you should ask your doctor for advice on driving and using machines.
This medicine contains alcohol. Therefore it may be unwise to drive immediately after a course of treatment.

Important information about some of the ingredients of Paclitaxel Injection
Paclitaxel Injection contains castor oil (50% polyethoxylated 35 caster oil) that may cause severe allergic reactions. If you are allergic to castor oil, **talk to your doctor before you receive Paclitaxel Injection.**

Paclitaxel Injection contains alcohol
This medicine contains 391mg of alcohol (ethanol) in each ml. The amount in of this medicine (at maximum dose of 220 mg/m^2) is equivalent to 646 ml beer or 258 ml wine.

The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.

If you are pregnant or breastfeeding, talk to your doctor or pharmacist before taking this medicine.

If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine

3. How to use Paclitaxel Injection

- **To minimise allergic reactions,** you will be given other medicines before you receive Paclitaxel Injection. These medicines can be given as either tablets or infusion into a vein or both.
- **You will receive Paclitaxel Injection as a drip** into one of your veins (by intravenous infusion), through an in-line filter. Paclitaxel Injection 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 Injection either alone or in combination with another anticancer agent.
- Paclitaxel Injection 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 Injection you need to receive.

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

If you are given more Paclitaxel Injection than you should
There is no known antidote for Paclitaxel Injection overdose. You will receive treatment of your symptoms.

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).
- These symptoms of neuropathy may persist beyond 6 months of treatment discontinuation.
- If you develop **severe or persistent diarrhoea**, with fever and stomach pain.

Very common (may affect more than 1 in 10 people)
- Minor allergic reactions such as flushing, rash, itching
- Infections: mainly upper respiratory infection, urinary tract infection
- Shortness of breath
- Sore throat or mouth ulcers, sore and red mouth, diarrhoea, feeling or being sick (nausea, vomiting)
- 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).
- Pain in the muscles, cramps, pain in the joints
- Fever, severe chills, headache, dizziness, tiredness, looking pale, bleeding, bruising more easily than normal
- Numbness, tingling or weakness in arms and legs (all symptoms of peripheral neuropathy) *
- Tests may show: reduction of blood platelet count, white or red blood cells count, low blood pressure

Common (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 (may affect up to 1 in 100 people)
- Shock due to infections (known as 'septic shock')
- Palpitations, cardiac dysfunction (AV block), rapid beating of the heart, heart attack, respiratory distress
- Fatigue, sweating, fainting (syncope), significant allergic reactions, inflammation of a vein caused by a blood clot (thrombophlebitis), swelling of the face, lips, mouth, tongue or throat
- Back pain, chest pain, pain around hands and feet, chills, abdominal (tummy) pain

- Tests may show: severe elevation of bilirubin (jaundice), high blood pressure, and blood clot.

Rare (may affect up to 1 in 1000 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
- 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 (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.

Not known (frequency cannot be estimated from the available data)
- Hardening/thickening of the skin (scleroderma)
- Sudden constriction of the muscles in the walls of the bronchioles (bronchospasm)
- Metabolic complications after cancer treatment (tumour lysis syndrome)Eye disorders, such as thickened and swollen macula (macular oedema), light flashes (photopsia) and spots, specks, flecks and “cobwebs” floating in your field of vision (vitreous floaters)
- Inflammation of veins (phlebitis)
- Systemic lupus erythematosus
- Serious condition that makes people bleed too easily, get blood clots too easily, or both (disseminated intravascular coagulation, 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

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

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 via

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 Injection

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 this medicine if you notice a cloudy solution or an insoluble precipitate.

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 Injection 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, 25, 50 and 100 ml (equivalent to 30, 100, 150, 300 and 600 mg of paclitaxel respectively).
- The other ingredients are polyoxyl 35 castor oil (macrogolglycerol ricinoleate 35) and anhydrous ethanol.

What Paclitaxel Injection looks like and contents of the pack
Paclitaxel Injection is a clear colourless to slightly yellow solution free from visible particles.

It is available in vials containing 5 ml, 16.7 ml, 25 ml, 50 ml and 100 ml of concentrate for solution for injection.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare Ireland Limited
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

Manufacturer:
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

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

Name of the member state	Name of the medicinal product
The Netherlands	Paclitaxel Accord 6 mg/ml, Concentraat voor oplossing voor intraveneuze infusie
Austria	Paclitaxel Accord 6 mg/ml, Konzentrat zur Herstellung einer Infusionslösung
Belgium	Paclitaxel Accord Healthcare 6 mg/ml, solution à diluer pour perfusion/ concentraat voor oplossing voor infusie / Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Paclitaxel Accord 6 mg/ml Concentrate for Solution for Infusion
Cyprus	Paclitaxel Accord 6 mg/ml, Concentrate for Solution for Infusion
Czech Republic	Paclitaxel Accord 6 mg/ml koncentrat pro pripravu infuzniho roztoku
Germany	Paclitaxel Accord 6 mg/ml, Konzentrat zur Herstellung einer Infusionslösung
Denmark	Paclitaxel Accord 6 mg/ml, Concentrate for Solution for Infusion
Estonia	Paclitaxel Accord 6 mg/ml
Spain	Paclitaxel Accord 6 mg/ml, concentrado para solucion para perfusion
Finland	Paclitaxel Accord 6 mg/ml, Infuusiokonsentraatti, Liuosta Varten / koncentrat till infusionsvätska, lösning
France	Paclitaxel Accord 6 mg/ml, Solution à diluer pour perfusion
Hungary	Paclitaxel Accord 6 mg/ml, Concentrate for Solution for Infusion
Ireland	Paclitaxel 6 mg/ml, Concentrate for Solution for Infusion
Italy	Paclitaxel Accord Healthcare 6 mg/ml, Concentrate for Solution for Infusion
Lithuania	Paclitaxel Accord 6 mg/ml, koncentratas infuziniam tirpalui
Latvia	Paclitaxel Accord
Norway	Paclitaxel Accord 6 mg/ml, Konsentrat til infusjonsvæke
Poland	Paclitaxelum Accord
Portugal	Paclitaxel Accord
Romania	Paclitaxel Accord 6 mg/ml, concentrat pentru soluţie perfuzabilă
Sweden	Paclitaxel Accord 6 mg/ml, Koncentrat till infusionsvätska, lösning
Slovenia	Paclitaxel Accord 6 mg/ml koncentrat za raztopino za infundiranje
Slovak Republic	Paclitaxel Accord 6 mg/ml, infúzny koncentrát
United Kingdom	Paclitaxel 6 mg/ml, Concentrate for Solution for Infusion

This leaflet was last revised in 09/2023.

The following information is intended for healthcare professionals only:

Preparation of infusion solutions:

- Containers and infusion sets used with Paclitaxel Injection 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 Injection** 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, the Paclitaxel Injection must be further diluted with either:
- 0.9% Sodium Chloride Injection
- 5 % Dextrose Injection
- 5% Dextrose and 0.9% Sodium Chloride injection
- 5% Dextrose in Ringer's Injection

The final infusion concentration of paclitaxel must range between 0.3 mg/ml and 1.2 mg/ml.
DEHP-free containers and infusion sets should be used.

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 H_2 antagonists prior to administration. Do not readminister Paclitaxel Injection until the neutrophil count is $\geq 1,500/mm^3$ ($\geq 1,000/mm^3$ for Kaposi's sarcoma patients) and the platelet count is $\geq 100,000/mm^3$ ($\geq 75,000/mm^3$ 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.

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 Injection 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 Injection are as follows:

Indication	**Dose**	**Interval between Paclitaxel Injection courses**
First-line ovarian carcinoma	135 mg/m^2 over 24 hours, followed by cisplatin 75 mg/m^2 or 175 mg/m^2 over 3 hours, followed by cisplatin 75 mg/m^2	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 Injection until the neutrophil count is ≥ 1,500/mm³ (≥ 1,000/mm³ for Kaposi's sarcoma patients) and the platelet count is ≥ 100,000/mm³ (≥ 75,000/mm³ for Kaposi's sarcoma patients).

Patients who experience severe neutropenia (neutrophil count < 500/mm³ 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 Injection (see Summary of Product Characteristics).

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