axionovo GMBH

axitaxel® 6 mg/ml concentrate for solution for infusion

Active substance: 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 inclused any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What axitaxel® 6 mg/ml is and what it is used for?

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

axitaxel® 6 mg/ml is used to treat:

Ovarian cancer:
- as first-line treatment (after previous surgery in combination with cisplatin, a platinum-containing medicine).
- after standard platinum-containing medicines have been tried but did not work.

Breast cancer:
- as first-line treatment of advanced disease or disease that has spread to other parts of the body (metastatic disease). axitaxel® 6 mg/ml is either combined with an anthracycline (e.g. doxorubicin) or with a medicine called trastuzumab (for patients for whom anthracyclines are not indicated and whose cancer cells have a surface protein called HER2, see the package leaflet of trastuzumab).
- as additional treatment after previous surgery, following anthracycline/cyclophosphamide treatment (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 are not indicated.

AIDS-associated Kaposi's sarcoma:
- where another treatment (e.g. liposomal anthracyclines) has been tried but did not work.

2. What you need to know before you use axitaxel® 6 mg/ml

You should not be given axitaxel® 6 mg/ml
- if you are allergic to paclitaxel or any of the other ingredients of this medicine listed in section 6, especially polyoxyethylated 35 castor oil (macrogolglycerol ricinoleate 35),
- if you do not have enough white blood cells. Your doctor will take blood samples to check this,
- if you are breast feeding,
- if you have a serious, uncontrolled infection and axitaxel® 6 mg/ml is being used to treat Kaposi's sarcoma.

If any of these apply to you, talk to your doctor before starting treatment with axitaxel® 6 mg/ml.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before using axitaxel® 6 mg/ml.

To reduce allergic reactions, you will be given other medicines before axitaxel® 6 mg/ml is administered.

Tell your doctor immediately if any of these apply to you:
- if you experience severe allergic reactions (e.g. 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, a sore throat, or mouth ulcers (signs of bone marrow suppression),
- if you experience numbness or weakness in your arms and legs (signs of peripheral neuropathy); a reduction in the dose of axitaxel® 6 mg/ml may be necessary,
- if you have serious liver problems; in this case, the use of axitaxel® 6 mg/ml is not recommended,
- if you have heart conduction problems,
- if you suffer from serious or persistent diarrhoea during or shortly after treatment with axitaxel® 6 mg/ml, accompanied by fever and abdominal pain. Your bowel might be inflamed (pseudomembranous colitis). If you have previously had chest X-ray (as this might increase the risk of pneumonia),
- if you have a sore or red mouth (signs of mucositis) and are treated for Kaposi's sarcoma. You may need a lower dose.

axitaxel® 6 mg/ml must always be infused into a vein. The infusion of axitaxel® 6 mg/ml into an artery may cause inflammation of the arteries and cause pain, swelling, redness and a feeling of heat.

Children and adolescents
axitaxel® 6 mg/ml is not recommended for use in children and adolescents (under 18 years of age).

Other medicines and axitaxel® 6 mg/ml
Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines, including medicines obtained without a prescription. This is because axitaxel® 6 mg/ml or the other medicine may then not work as well as expected or the occurrence of a side effect may become more likely.

Interaction means that different medicines can affect each other. It could be that other medicines then do not work as well as expected or the occurrence of a side effect becomes more likely.
Therefore, your doctor needs to know if axitaxel® 6 mg/ml is used together with the following medicines:

- **Cisplatin** (used to treat cancer): axitaxel® 6 mg/ml must be administered before cisplatin. Your kidney function might need to be checked more frequently.
- **Doxorubicin** (used to treat cancer): axitaxel® 6 mg/ml must be administered 24 hours after doxorubicin to prevent high doxorubicin levels in your body.

Talk to your doctor if you are taking paclitaxel at the same time as the following preperations:

- medicines used to treat infections (eg. antibiotics such erythromycin, rifampicin, etc.; ask your doctor, nurse or pharmacist if you are not sure whether the medicine you are taking is an antibiotic), including medicines used to treat fungal infections (e.g. ketoconazole)
- mood stabilisers, sometimes also called anti-depressants (e.g. fluoxetine)
- medicines used to treat seizures (epilepsy) (e.g. carbamazepine, phenytoin)
- medicines used to help you lower blood fat 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.

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
axitaxel® 6 mg/ml must not be used during pregnancy unless clearly necessary.

Breest-feeding
If you are treated with axitaxel® 6 mg/ml, you must not breast-feed for the entire treatment. Do not restart breast-feeding unless your doctor has allowed you to.

Fertility
This medicine may cause birth defects if used during conception by either parent or during pregnancy. 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 should seek counselling on sperm preservation before treatment with axitaxel® 6 mg/ml, due to possible infertility.

Driving and using machines
This medicine contains alcohol. Hence, it is not advisable to drive immediately after a course of treatment. Do not drive under any circumstances if you feel lightheaded or unsteady.

Important information about some of the ingredients of axitaxel® 6 mg/ml
- axitaxel® 6 mg/ml contains castor oil (50 % macrogolglycerol ricinoleate) that may cause serious allergic reactions. If you are allergic to castor oil, talk to your doctor before you receive axitaxel® 6 mg/ml.
- axitaxel® 6 mg/ml contains alcohol (approximately 50 % ethanol) - each milliliter of axitaxel® 6 mg/ml contains about 0.4 g alcohol. One axitaxel® 6 mg/ml dose of 300 mg/50 ml contains 20 g alcohol. This is equivalent to to 450 ml beer or 175 ml wine.

3. How to use axitaxel® 6 mg/ml?

To minimise allergic reactions, you will be given other medicines before you receive axitaxel® 6 mg/ml. These medicines can be given as either tablets or infusion into a vein.
You will receive axitaxel® 6 mg/ml as a drip into one of your veins (by intravenous infusion), through an in-line filter. axitaxel® 6 mg/ml 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 axitaxel® 6 mg/ml either alone or in combination with another anticancer agent.
axitaxel® 6 mg/ml 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 axitaxel® 6 mg/ml you need to receive.

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

If you are given more axitaxel® 6 mg/ml than you should
There is no known antidote for an overdose of axitaxel® 6 mg/ml. You will receive treatment for 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 get signs of an allergic reaction. These signs may include:
- Flushing
- Skin reactions
- Itching
- Chest tightness
- Shortness of breath or difficulty breathing
- Swelling

These can all be signs of serious side effects.

Tell your doctor immediately
- if you have fever, severe chills, a sore throat, or mouth ulcers (signs of bone marrow suppression).
- if you feel numbness or weakness in your arms and legs (signs of peripheral neuropathy).
- if you suffer from severe or persistent diarrhoea accompanied by fever and abdominal pain.

Very common (may affect more than 1 in 10 people):
- Mild allergic reactions with flushin, rash, itching
- Infections: mainly upper respiratory tract infections, urinary tract infections
- Shortness of breath
- Sore throat or mouth ulcers, inflamed and red mouth, diarrhoea, feeling sick (nausea, vomiting)
- Hair loss (the majority of cases of hair loss occurred less than one month after the start of paclitaxel; when it occurs, hair loss is pronounced in most patients (more than 50%))
- Muscle pain, cramps, joint pain
- Fever, severe chills, headache, dizziness, tiredness, pale skin, bleeding, bruising more easily than normal
- Numbness, tingling or weakness in arms and legs (these are signs of peripheral neuropathy)*
- Tests may reveal the following: decrease in the platelet count, white or red blood cell counts, low blood pressure

* Can persist beyond 6 months of paclitaxel discontinuation.

Common (may affect up to 1 in 10 people):
- Mild temporary changes to the nails and skin, injection site reactions (swelling, pain, and skin redness at the injection site)
- Tests may reveal the following: slower heart rate, sharp increase 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").
- Heart attackpalpitations, heart dysfunction (AV block), rapid heartbeat, shortness of breath
- Heart muscle disease (cardiomyopathy)
- Fatigue, sweating, fainting (syncope), significant allergic reactions, phlebitis (inflammation of the veins), swelling of the face, lips, mouth, tongue, or throat
- Back pain, chest pain, pain around hands and feet, chills, abdominal pain
- Tests may reveal the following: sharp increase of bilirubin (a sign of jaundice), high blood pressure, blood clots

Rare (may affect up to 1 in 1 000 people):
- Decrease in white blood cells with fever and increased risk of infection (febrile neutropenia)
- Nerve disorder with feelings of weakness in the arm and leg (motor neuropathy)
- Shortness of breath, pulmonary embolism, lung

fibrosis, dyspnea, pleural effusion
- Bowel obstruction, bowel perforation), inflammation of the colon (ischaemic colitis), inflammation of the pancreas (pancreatitis)
- Itching, rash, skin redness (erythema)
- Blood poisoning (sepsis), peritonitis, pneumonia
- Fever, dehydration, weakness, oedema, malaise
- Serious and potentially fatal hypersensitivity reactions (anaphylactic reaction)
- Tests may reveal the following: increased creatinine in the blood, indicating impaired kidney function
- Heart failure

Very rare (may affect up to 1 in 10 000 people:
- Irregular rapid heart rhythm (atrial fibrillation, supraventricular tachycardia)
- Sudden dysfunction of the blood-forming cells (acute myeloid leukaemia, myelodysplastic syndrome). Disturbances of the optic nerve and vision (scintillating scotoma)
- Seizures (grand mal fits, convulsions), nerve disorder (autonomic neuropathy), brain disease (encephalopathy), dizziness, impaired coordination, headache
- Hearing loss or reduction of hearing (ototoxicity), ringing in the ears (tinnitus), vertigo
- Cough
- Blood clot in a blood vessel of the abdomen and bowel (mesenteric thrombosis), inflammation of colon, sometimes with persistent severe diarrhoea (pseudomembranous colitis, neutropenic colitis), dropsy (ascites), oesophagitis, constipation
- Serious hypersensitivity reactions with fever, skin redness, pain in the joints and/or inflammation of the eyes (Stevens-Johnson syndrome), localised peeling of the skin (epidermal necrolysis), redness with irregular red (weeping) patches (erythema multiforme), inflammation of the skin with blisters and peeling (exfoliative dermatitis), hives, nail loss (patients should wear sunblock on their hands and feet during treatment)
- Loss of appetite (anorexia)
- Serious and potentially fatal hypersensitivity reactions with shock (anaphylactic shock)
- Impaired liver function (hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome))
- States of confusion

Not known (frequency cannot be estimated based on the available data):
- Hardending/thickening of the skin (sclerodema)
- "Butterfly rash" (systemic lupus erythematosus)
- Tumour lysis syndrome
- Fluid accumulation in the macula of the eye (macular oedema), perception of light phenomena, such as flashes of light in the eye (photopsia), deposits in the vitreous body of the eye (vitreous opacity)
- Inflammation of the veins (phlebitis)
- Disseminated intravascular coagulation, or "DIG", has been reported. This is a serious disease, causing people to bleed too easily or form 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

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

5. How to store axitaxel® 6 mg/ml?

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

Storage conditions

Do not store above 25 °C. Store in the original package in order to protect from light.

6. Contents of the package and other information

What axitaxel® 6 mg/ml contains

The active substance is: Paclitaxel
1 ml concentrate for solution for infusion contains 6 mg of paclitaxel.
One 5 ml vial contains 30 mg paclitaxel.
One 16.7 ml vial contains 100 mg paclitaxel.
One 50 ml vial contains 300 mg paclitaxel.

The other ingredients are:

Macrogolglycerol ricinoleate 35 (Ph.Eur.), ethanol (395 mg/ml), citric acid, nitrogen.

What axitaxel® 6 mg/ml looks like and contents of the pack

axitaxel® 6 mg/ml is a clear, colourless to slightly yellow, viscous solution.
Folding box containing 1 vial with 30 mg paclitaxel in 5 ml solution
Folding box containing 1 vial with 100 mg paclitaxel in 16.7 ml solution
Folding box containing 1 vial with 300 mg paclitaxel in 50 ml solution

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

AxioNovo GmbH.
Kammerichstrasse 39
33647 Bielefeld
Germany
Phone: +49 521 988 35 - 0
Fax: +49 521 988 35 - 18
E-mail: info@axionovo.de

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The following information is intended for healthcare professionals only:

Handling:

Paclitaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling paclitaxel. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. Contact of paclitaxel with skin and mucous membranes should be avoided.
If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat, and nausea have been reported.
Refrigerated storage of the unopened vials can lead to precipitation, which dissolves at room temperature by gentle shaking or spontaneously. This will not affect the quality of the medicinal product. If streaks persist or if an insoluble precipitate is observed, the vial must be discarded.

300 mg vial axitaxel® 6 mg/ml: Even after repeated piercing and repeated withdrawal of the product, the paclitaxel concentrate remains microbially, chemically and physically stable at 25 °C for up to 28 days. Other storage times and conditions of the opened medicinal product are the responsibility of the user.
Do not use Chemo Pin or similar aids with spikes, as this can damage the rubber stopper of the vial, resulting in loss of sterility.

Preparation of the infusion solution:

Prior to use, axitaxel® 6 mg/ml must be diluted under aseptic conditions with one of the following solvents:
- 0.9 % sodium chloride solution
- 5 % glucose solution
- 5 % glucose solution and 0.9 % sodium chloride solution
- 5 % glucose solution in Ringer's solution

The final concentration of paclitaxel in the solution for infusion must be between 0.3 mg/ml and 1.2 mg/ml. The chemical and physical stability of the ready-to-use solution after dilution with 0.9 % sodium chloride solution, 5 % glucose solution, 5 % glucose solution plus 0.9 % sodium chloride solution (1:1), or 5 % glucose solution in Ringer's solution (1:1), has been demonstrated for 72 hours at 25 °C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions are the responsibility of the user. Diluted solutions must not be stored in the refrigerator.
During reconstitution, the solution may produce streaks due to the solvent in the concentrate; these cannot be removed by filtration. The reconstituted axitaxel® 6 mg/ml solution for infusion should be infused via an in-line filter with a microporous membrane with a pore diameter of ≤ 0.22 µm.
In rare cases, precipitation has been reported during the axitaxel® 6 mg/ml infusion, usually towards the end of a 24-hour infusion. The cause of this precipitation is unclear, but it is thought to be associated with supersaturation of the diluted solution for infusion. To reduce the risk of precipitation, axitaxel® 6 mg/ml should be administered as soon as possible after preparation of the diluted solution for infusion. Excessive shaking should be avoided. Infusion sets should be thoroughly rinsed before use. During the infusion, the appearance of the solution should be inspected regularly. The infusion must be stopped if precipitation occurs.
Containers and infusion sets used with axitaxel® 6 mg/ml must be DEHP-free. This is to minimise patient exposure to DEHP [di-(2-ethylhexyl) phthalate], a plasticiser which may be leached out of PVC infusion bags or sets. The use of infusion filters (e.g. IVEX-2) with short PVC inlet and/or outlet section did not lead to any significant release of DEHP.

Disposal:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic substances.

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