axionovo GMBH

axiplatin® 5 mg/ml concentrate for solution for infusion

Active substance: Oxaliplatin

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.

What is in this leaflet

1. What axiplatin® is and what it is used for

The active ingredient of axiplatin® is oxaliplatin.

axiplatin® is used to treat cancer of the large bowel (treatment of stage III colon cancer after complete resection of primary tumour, metastatic cancer of colon and rectum). axiplatin® is used in combination with other anticancer medicines called 5-fluorouracil and folinic acid.

axiplatin® is an antineoplastic or anticancer medicine and contains platinum.

2. What you need to know before you use axiplatin®

Do not use axiplatin®,

- if you are allergic to oxaliplatin or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.
- if you already have a reduced number of blood cells.
- if you already have tingling and numbness in the fingers and/or toes and have difficulty performing. delicate tasks, such as buttoning clothes.
- if you have severe kidney problems.

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before using axiplatin®,

- if you have moderate or mild kidney problems.
- if you have ever suffered an allergic reaction to platinum-containing medicines (e.g. carboplatin or cisplatin). Allergic reactions can occur during any oxaliplatin infusion.
- if you have any liver problems.
- if you are pregnant or planning a pregnancy. It is very important that you discuss this with your doctor **before** you receive any treatment.

If any of the following applies to you at any time, tell your doctor immediately. Your doctor may need to treat you for these events. Your doctor may need to reduce the dose of axiplatin®, or delay or stop your treatment with axiplatin®

- If you have an unpleasant sensation in the throat, in particular when swallowing, and have a sensation of shortness of breath, during the treatment, tell your doctor.
- If you have nerve problems in your hands or feet, such as numbness or tingling, or decreased sensations in your hands or feet, tell your doctor.
- If you have headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss, tell your doctor.
- If you feel or are sick (nausea or vomiting), tell your doctor.
- If you have severe diarrhoea, tell your doctor.
- If you have sore lips or mouth ulcers (mucositis/ stomatitis), tell your doctor.
- If you have a reduction in white blood cells or platelets, tell your doctor. Your doctor may reduce the dose of axiplatin® postpone your treatment with oxaliplatin.
- If you have unexplained respiratory symptoms such as cough, or any difficulties in breathing, tell your doctor. Your doctor may stop your treatment with oxaliplatin.
- If you develop an extreme tiredness, shortness of breath, or kidney disease where you pass little or no urine (symptoms of acute renal failure), tell your doctor.

Children and adolescents

axiplatin® is intended only for adults.

Other medicines and axiplatin®

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

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

It is not recommended that you become pregnant during treatment with oxaliplatin and you must use an effective method of contraception. Female patients should take appropriate contraceptive measures during and after therapy continuing for 4 months.

If you are pregnant or planning a pregnancy it is very important that you discuss this with your doctor **before** you receive any treatment.

If you get pregnant during your treatment, you must immediately inform your doctor.

Breast-feeding

You must not breast-feed while on treatment with axiplatin®.

Fertility

Oxaliplatin can cause infertility, which may be irreversible. Male patients are therefore advised not to father children during and up to 6 months after the treatment and to seek advice on conservation of sperm prior to treatment. Male patients should take appropriate contraceptive measures during and after therapy continuing for 6 months.

Driving and using machines

Treatment with Oxaliplatin involves an increased risk of dizziness, nausea and vomiting, and other neurological symptoms that affect walking and balance. If this happens you should not drive or operate machinery. If you have vision problems while taking this medicine, do not drive, operate machinery or engage in potentially dangerous activities.

3. How to use axiplatin®

axiplatin® is intended only for adults.
For single use only.

Dose

The dose depends on the body surface area (calculated in m^2), which is determined from your height and weight. In addition the dose depends on the results of blood tests and whether you have previously experienced side effects with oxaliplatin. The usual dose for adults, including elderly patients, is 85 mg/m^2 body area.

Method and route of administration

axiplatin® will be prescribed to you by a doctor with experience in the treatment of cancer.
You will be treated by a healthcare professional, who will have made up the required dose of axiplatin®.
axiplatin® is given by slow injection into a vein (intravenous infusion) over a 2-to-6-hour period.
axiplatin® will be given to you at the same time as folinic acid and before the infusion of 5-fluorouracil.

You should usually receive your infusion once every 2 weeks.

Duration of use

The duration of therapy will be decided by your doctor. Your treatment will last a maximum of 6 months when used after complete removal of your tumour.

If you use more axiplatin® than you should

As this medicine is administered by a healthcare professional, it is highly unlikely that you have received too much or too little. However, do inform your doctor if you have any concerns. In case of overdose, you may experience increased side effects. Your doctor will give you appropriate treatment for these side effects. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Inform your doctor immediately if you notice any of the following side effects:

- Symptoms of an allergic or anaphylactic reaction with sudden signs such as rash, itching or hives on the skin, difficulties in swallowing, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, extreme tiredness (you may feel you are going to faint). In the majority of cases, these symptoms occurred during the infusion or immediately after but delayed allergic reactions have also been observed hours or even days after the infusion.
- Abnormal bruising, bleeding, or signs of infection such as a sore throat and high temperature.
- Persistent or severe diarrhoea or vomiting.
- Presence of blood or dark brown coffee-coloured particles in your vomit.
- Sore lips or mouth ulcers (stomatitis/mucositis).
- Unexplained respiratory symptoms such as dry cough, difficulties in breathing or crackles.
- Swelling of the hands, feet, ankles, face, lips, mouth, or throat (which may cause difficulty swallowing or breathing) - symptoms of angioedema.
- A group of symptoms such as headache, altered mental functioning, seizures and abnormal vision from blurriness to vision loss (symptoms of reversible posterior leukoencephalopathy syndrome, a rare neurological disorder).
- Extreme tiredness with decreased number of red blood cells, and shortness of breath (haemolytic anaemia), alone or combined with low platelet count, abnormal bruising (thrombocytopenia) and kidney disease where you pass little or no urine (symptoms of haemolytic-uraemic syndrome).

Other known side effects of axiplatin® are:

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

- axiplatin® can affect the nerves (peripheral neuropathy). You may feel a tingling and/or numbness in the fingers, toes, around the mouth, or in the throat, which may sometimes occur in association with cramps. These symptoms are often provoked by exposure to cold, for example by opening the refrigerator or holding a cold drink. You may also experience difficulties with the performance of fine motor movements such as buttoning up clothing. Even though in the majority of cases these symptoms disappear completely, there is a possibility that they will persist after the end of the treatment.
- Some people have experienced a tingling, shock-like sensation passing down the arms or trunk when the neck is flexed.
- Oxaliplatin may sometimes cause an unpleasant sensation in the throat, which is especially noticeable on swallowing and which gives an impression of shortness of breath. If this occurs, it usually does so during or within a few hours after the end of the infusion, and is triggered by exposure to cold. This unpleasant phenomenon does not last long and regresses without needing any treatment. Your doctor will decide on any adjustment of treatment.
- Oxaliplatin causes temporary reduction in the number of blood cells. The reduction of red cells may cause anaemia (a reduction of red cells), abnormal bleeding or bruising (due to a reduction in platelets). The reduction in white blood cells may make you prone to infections. Your doctor will take blood to check that you have sufficient blood cells before you start treatment and before each subsequent course.
- Allergic reactions – red itching rash, swelling of the hands, feet, ankles, face, lips, mouth, and the throat (which can lead to difficulties in breathing and swallowing), which may produce a sensation of incipient loss of consciousness.
- Complete or partial loss of appetite.
- High levels of blood glucose (blood sugar), which can cause a strong thirst, a dry mouth, or an increased frequency of passing urine.
- Irregular heartbeat (caused by a low level of potassium in blood).
- Tiredness, disorientation, muscle twitching, cramp attacks, and profound coma (caused by a low level of sodium in blood).
- Disturbances of the sense of taste.
- Headaches.
- Shortness of breath/dyspnoea.
- Cough.
- Nosebleeds.
- Nausea and vomiting – to avoid these effects you will usually be given medication by your doctor before, and if necessary, also after the treatment.
- Diarrhoea. Contact you doctor without delay if the diarrhoea or vomiting is persistent or severe.
- Stomatitis/mucositis (sore lips or mouth ulcers).
- Abdominal pains, constipation.
- Skin disorders.
- Loss of hair (alopezia)
- Backache.
- Tiredness, loss of strength, sensation of weakness, pains in the whole body.
- Pain or skin reddening both around and directly at the injection site during the infusion.
- Fever, rigors (tremors).
- Alteration in blood tests including those relating to abnormalities in liver function.
- Weight gain.

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

- Infection due to a reduction in white blood cells.
- Inflammation of nasal mucous membranes.
- Respiratory tract infection.
- Loss of fluid with tissue dehydration.
- Dizziness.
- Swelling of muscle-supplying nerves.
- Stiff neck, light intolerance, aversion to dazzling light, headaches.
- Conjunctivitis, visual disturbances.
- Abnormal bleeding.
- Blood clot formation, usually in a leg, with painful swelling and reddening.
- High blood pressure.
- Blood clot in the lung, causing chest pains and breathlessness.
- Attacks of skin reddening.
- Pains in the chest, hiccups.
- Digestive disturbances, heartburn, blood in stool.
- Digestive disturbances, heartburn.
- Peeling skin, rash, increased sweating and nail disorders.
- Pains in the joints and bones.
- Blood in urine, pains when passing urine or a change in urination frequency.
- Blood tests showing a change in kidney function.
- Loss of weight.
- Depression.
- Sleep disturbances.
- Fall.

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

- Hearing disturbances.
- Impaired or blocked bowel passage due to intestinal obstruction/swelling.
- Nervousness.
- Higher acidity of the blood.

Rare (may affect up to 1 in 1 000 people):

- Indistinct speech.
- Seizures, hypertension, headache, confusion, blindness and other visual or nervous system disorders as symptoms of reversible posterior leukoencephalopathy syndrome (RPLS or posterior reversible

encephalopathy syndrome, PRES).
- Deafness.
- Scarring and thickening in the lungs with difficulties in breathing, sometimes fatal (interstitial lung disease).
- Inflammation causing abdominal pains and diarrhoea.
- Pancreatitis.
- Reversible short-term loss of vision.

Very rare (may affect up to 1 in 10 000 people):
- Liver disorders, for which your doctor will be watching out.
- Changes in kidney function.

Not known (frequency cannot be estimated from the available data):
- Seizures/uncontrolled shaking of the body (convulsion).
- Spasmodic constriction of the larynx that can cause difficulty breathing (laryngospasm).
- Extreme tiredness with decreased number of red blood cells, and shortness of breath (haemolytic anaemia), alone or combined with low platelet count and kidney disease where you pass little or no urine (symptoms of Haemolytic-uraemic syndrome), which may be fatal, have been reported.
- Allergic vasculitis (inflammation of blood vessels).
- Autoimmune reaction leading to reduction of all blood cell lines (autoimmune pancytopenia).
- Myocardial infarction (heart attack), angina pectoris (pain or uncomfortable feeling in the Chest).
- Oesophageal inflammation (inflammation of the lining of the esophagus - the tube that connects your mouth with your stomach- resulting in pain and swallowing difficulty).

Side effect reporting
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 axiplatin®

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 label and the carton after "EXP". The expiry date refers to the last day of that month.

Prior to mixing keep this medicine in the outer carton in order to protect from light. Do not freeze.

axiplatin® should not come into contact with the eyes or skin. If there is any accidental spillage, tell the doctor or medicinal health care professional immediately.

This medicine is for single use only. When the infusion has finished, axiplatin® will be disposed carefully by the doctor or health care professional.

After dilution in 5 % glucose solution (50 mg/ml), chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C and for 6 hours at 25 °C.
From a microbiological point of view, the infusion preparation should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C unless dilution has taken place in controlled and validated aseptic conditions

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 axiplatin® contains
- The active substance is: oxaliplatin. 1 ml of the concentrate for solution for infusion contains 5 mg oxaliplatin.
- Each vial of 10 ml of the concentrate contains 50 mg oxaliplatin.
- Each vial of 20 ml of the concentrate contains 100 mg oxaliplatin.
- Each vial of 40 ml of the concentrate contains 200 mg oxaliplatin.

- The other ingredient is water for injections.

What axiplatin® looks like and contents of the pack
axiplatin® is a clear, colourless concentrate for solution for infusion.

Pack sizes
Packs with 1 vial containing 10 ml, 20 ml or 40 ml of concentrate.

Not all pack sizes may be marketed.

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The following information is intended for healthcare professionals only:

Handling instructions for safe use
Like other potentially toxic substances, oxaliplatin solutions must be prepared and handled with due care.

The handling of this cytotoxic agent by medical health care professionals requires all safety measures ensuring protection of the user and his/her environment.

Injection solutions of cytotoxic medicinal products must be prepared by specially trained personnel familiar with the medicinal product used, under conditions guaranteeing protection of the environment, and especially protection of the personnel involved in accordance with the hospital's standard procedures. This requires the provision of a working area designated for this purpose, in which smoking, eating, and drinking are prohibited. The personnel must be provided with suitable working equipment, and in particular with long-sleeve laboratory coats, protective masks, head coverings, protective goggles, sterile disposable gloves, protective workplace coverings, containers, and collection bags for waste. Excrement and vomit must be handled with care.

Pregnant women must be warned against handling cytotoxic substances and must avoid them.

Any broken containers must be handled with the same care and treated as contaminated waste. Contaminated waste should be placed in solid suitably labeled containers for disposal by incineration. See below chapter "Waste disposal".
If oxaliplatin concentrate for solution for infusion should come into contact with skin, wash immediately and thoroughly with water. If oxaliplatin concentrate for solution for infusion should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for use
- The product MUST NOT be used with aluminum-containing injection equipment.
- The product MUST NOT be administered undiluted.
- Only glucose 5 % (50 mg/ml) infusion solution is to be used as a diluent. The product MUST NOT be diluted with sodium chloride or chloride-containing solutions.
- The product MUST NOT be mixed with any other medicinal products in the same infusion bag or administered simultaneously in the same infusion line.
- The product MUST NOT be mixed with alkaline medicinal agents or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other active ingredients. Alkaline medicinal agents or solutions will adversely affect the stability of oxaliplatin.

Instructions for use with folinic acid (e.g. with calcium folinate or disodium folinate)
250 to 500 ml of 5 % (50 mg/ml) glucose infusion solution containing 85 mg/m² oxaliplatin is infused simultaneously by the i.v. route with the folinic acid infusion solution (folinic acid in 5 % glucose) using a Y-line placed immediately before the site of infusion, over a period of 2 to 6 hours. The two medicines must not be mixed in the same infusion bag. For dilution of folinic acid only isotonic 5 % glucose solution may be used. Never use any alkaline or sodium chloride solution, or any other solution containing chloride for dilution.

Instructions for use with 5-fluorouracil
Oxaliplatin should always be administered before fluoropyrimidines, e.g. 5-fluorouracil

After the administration of Oxaliplatin the access must be rinsed through before the administration of 5-fluorouracil. For further information on medicinal products given in combination with oxaliplatin, see the corresponding Summary of Product Characteristics.

Inspect visually prior to use. Only clear solutions without particles should be used.
The medicinal product is for single use only. Any unused infusion solution should be discarded (see chapter "Waste disposal" below).

Preparation of the infusion solution
Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a glucose 5 % (50 mg/ml) solution to give an oxaliplatin concentration between 0.2 mg/ml and 0.7 mg/ml. Over this concentration range the physicochemical stability of oxaliplatin has been demonstrated.

Administer by intravenous infusion.

After dilution in glucose 5 % (50 mg/ml) solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C and for 6 hours at 25 °C.
From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused infusion solution should be discarded.

NEVER use sodium chloride or chloride containing solutions for dilution.
The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.

Infusion of the solution
The administration of oxaliplatin does not require prehydration.
Oxaliplatin diluted in 250 to 500 ml of a glucose 5 % (50 mg/ml) solution to give a concentration not less than 0.2 mg/ml must be infused either by peripheral vein or central venous line over 2 to 6 hours.
When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Waste disposal
Remnants of this medicinal product and all material used for dilution and administration must be destroyed in accordance with the hospital's standard procedures for cytotoxic substances and local requirements for disposal of hazardous waste.

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