Package leaflet: Information for the patient

Epimedac 2 mg/ml solution for injection

epirubicin hydrochloride

Read all of this leaflet carefully before you are given 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 Epimedac is and what it is used for

Epirubicin hydrochloride – the active substance of Epimedac – belongs to a group of active substances called anthracyclines. These cell-destroying (cytotoxic) active substances are used to treat cancer.

Epimedac is used in the treatment of
- breast cancer,
- advanced ovarian cancer,
- stomach cancer,
- small cell lung cancer (special form of lung cancer),
- superficial or very localised cancer of the bladder.

2. What you need to know before you are given Epimedac

You must not be given Epimedac if you
- are allergic to epirubicin hydrochloride or any of the other ingredients of this medicine (listed in section 6) or to anthracyclines (e.g. doxorubicin and daunorubicin).
- are allergic to anthracenediones (a group of medicines used to treat cancer).
- have a persistent inhibition of blood-cell production in the bone marrow due to previous treatment with other cytotoxic medicines or radiotherapy.
- have been given the maximum dose of epirubicin or other anthracyclines (e.g. doxorubicin and daunorubicin) and anthracenediones (medicines used to treat cancer).
- have or have previously had heart problems (e.g. heart rhythm disorders, reduced heart function, heart attack, heart muscle disorder, acute inflammation of the heart, unstable angina pectoris).
- have severe liver problems.
- suffer from a systemic infection (infection which affects the whole organism).
- are breast-feeding.
- have severe inflammation of the mouth lining and/or stomach lining.

For use in the bladder, you must not be given Epimedac if
- you have an infection of the urinary tract.
- the tumour has penetrated the bladder wall.
- there are problems inserting the catheter into the bladder.
- you suffer from a bladder infection.

- you have blood in your urine.
- you have a contracted bladder.
- there is a large volume of urine left in your bladder after you attempt to empty it.

Warnings and precautions
Special care is needed (check with your doctor) if
- your liver or kidneys are not working properly.
- you notice a sensation of discomfort close to or at the injection site during the infusion (the solution for injection may have leaked into the surrounding tissue).
- your numbers of white and red blood cells and platelets are reduced.
- you suffer from stomatitis or mucositis (sore lips or mouth ulcers).
- you have previously received radiotherapy of the breast or medicines that might have side effects on your heart.
- you have recently received or want to receive any vaccination in the near future.
- you have previously received trastuzumab (a medicine used to treat cancer).

Children
The safety and efficacy of Epimedac in children have not been established.

Other medicines and Epimedac
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, particularly the following:
- other medicines that may affect your heart; for example other cancer treatments (such as 5-fluorouracil, cyclophosphamide, cisplatin, taxanes) or calcium channel blockers (e.g. verapamil, dexverapamil) as well as concomitant or prior radiotherapy.
- other medicines that may affect your liver function.
- cimetidine (a medicine usually used to treat stomach ulcers and heartburn); cimetidine can make the effects of epirubicin stronger.
- paclitaxel (medicine used for cancer): there should be an interval of at least 24 hours between the epirubicin and the paclitaxel treatment.
- docetaxel (medicine used for cancer).
- quinine (medicine used for the treatment of malaria and for leg cramps).
- interferon alfa-2b (a medicine used in some cancers and lymphomas and for some forms of hepatitis).
- medicines which can affect the blood cell counts (for example other cytotoxic medicines, antibiotics such as sulphonamides and chloramphenicol, medicines for epilepsy such as diphenylhydantoin, antiretroviral medicines used to treat HIV infections, and painkillers such as aminopyrine derivatives).
- dexrazoxane (used to prevent chronic cumulative cardiotoxicity caused by epirubicin).
- trastuzumab. Trastuzumab (a medicine used in the treatment of certain cancers) can take up to 7 months to be removed from the body. As trastuzumab may affect the heart, you should not use epirubicin for up to 7 months after you have stopped taking trastuzumab. If epirubicin is used before this time, then your heart function should be carefully monitored.
- antibiotics such as sulphonamides and certain diuretics ("water tablets"); can lead to increased levels of uric acid in the blood.
- heparin (medicine that prevents the blood from clotting); can lead to loss of effectiveness of both epirubicin and heparin.

If you need to have any vaccinations, you must inform your doctor that you are being treated with epirubicin before receiving the vaccination.

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.

Epirubicin hydrochloride – the active substance in Epimedac – may cause birth defects, so it is important to tell your doctor if you think you are pregnant. In pregnant women, there have been some

reports associating epirubicin with heart problems in newborn and unborn babies, including reports of death of the foetus. You must not be given Epimedac during pregnancy unless clearly indicated by your doctor. Avoid becoming pregnant while you are taking or your partner is taking Epimedac. Women of childbearing age should use a reliable method of contraception during treatment with epirubicin and for at least 7 months after the final dose. Men should use a reliable method of contraception during treatment and for at least 4 months after the final dose. If you get pregnant during treatment with Epimedac, you are recommended to seek genetic counselling.
Men who wish to father children in the future should seek advice about freezing sperm before treatment with Epimedac is started.

You must discontinue breast-feeding before and during therapy with Epimedac and for at least 7 days after the final dose, as Epimedac can harm a breast-fed child.

Driving and using machines
Epimedac may cause nausea and vomiting, which can temporarily affect your ability to drive and use machines.

Epimedac contains sodium
This medicinal product contains 0.154 mmol (or 3.54 mg) sodium per ml of solution for injection. The different pack sizes of Epimedac contain the following amounts of sodium:

5 ml vial: This pack size contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

10 ml vial: This pack size contains 35.42 mg sodium (main component of cooking/table salt). This is equivalent to 1.77% of the recommended maximum daily dietary intake of sodium for an adult.

25 ml vial: This pack size contains 88.55 mg sodium (main component of cooking/table salt). This is equivalent to 4.43% of the recommended maximum daily dietary intake of sodium for an adult.

50 ml vial: This pack size contains 177.1 mg sodium (main component of cooking/table salt). This is equivalent to 8.86% of the recommended maximum daily dietary intake of sodium for an adult.

100 ml vial: This pack size contains 354.21 mg sodium (main component of cooking/table salt). This is equivalent to 17.71% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Epimedac is given

Epimedac will only be given to you under supervision of a doctor specialised in this type of treatment. Before and during treatment with Epimedac, your doctor will check various laboratory parameters (e.g. blood cell count, blood uric acid level, your liver function) and carefully monitor your heart function. Monitoring of the heart function will be continued for several weeks following the end of treatment with Epimedac.

The dose of Epimedac depends on the condition you are treated for, your response to therapy and other medicines you are given.

The dose of Epimedac is based on your body surface area. This is calculated from your height and weight.

The recommended dose of Epimedac is 60 – 90 mg per square metre of body surface area. It is given as an intravenous injection, i.e. into a blood vessel, over three to five minutes. You will receive an injection every three weeks.

In the treatment of small cell lung cancer, a higher dose of 120 mg per square metre of body surface area is given by injection into a vein over three to five minutes or as an infusion (drip) of up to 30 minutes, every three weeks.

For the treatment of breast cancer your doctor will decide on the dose and treatment regimen.

The dose will be reduced if you have a low level of white blood cells and platelets in your body, if you have liver or kidney problems, or if the medicine is used in combination with other cytotoxic medicines.

Epimedac can also be given directly into the bladder to treat superficial bladder cancer or to stop recurrence after bladder surgery to remove the cancer. The dose will depend upon the type of bladder cancer.
To avoid undue dilution of Epimedac with urine you are advised not to drink 12 hours before the treatment.

Your general condition will be closely observed before, during and after the treatment with Epimedac.

If you are given more Epimedac than you should
In case you were given a higher dose of Epimedac than required, you may feel symptoms such as severe problems with your heart, highly decreased count of blood cells, severe inflammation of the mouth and stomach lining and severe circulation problems. The occurring side effects may be more severe.
If such symptoms occur, Epimedac will be stopped immediately and your symptoms will be treated. In case of severe heart problems, a specialist for heart diseases may be contacted. In case of highly decreased blood cells, you may receive blood transfusions.

4. Possible side effects

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

Please tell your doctor immediately if you notice any side effects to discuss any further actions.

For one or two days after you have been given Epimedac your urine may have a red colour. This is normal and nothing to worry about.

Very common: may affect more than 1 in 10 people
- Infection
- Inhibition of blood-cell production in the bone marrow (myelosuppression), decreased number of white blood cells (leukopenia), decreased number of a special form of white blood cells (granulocytopenia and neutropenia), decreased number of red blood cells (anaemia) and low level of certain white blood cells accompanied by fever (febrile neutropenia), decreased number of platelets (thrombocytopenia)
- Inflammation of a mucous membrane (mucositis), inflammation inside the mouth (stomatitis), being sick (vomiting), watery stools or frequent bowel movements (diarrhoea), feeling sick (nausea), which can result in loss of appetite and abdominal pain
- Hair loss, normally reversible
- Red colouration of urine for 1 to 2 days after the treatment
- Absence of menstruation
- Pink eye (conjunctivitis), inflammation of the cornea of the eye (keratitis)

- Hot flushes
- Skin lesion
- Vein inflammation (phlebitis)
- Feeling of discomfort (malaise), fever
- Changes in the level of certain liver enzymes (so-called transaminases)
- Bladder infection (chemical cystitis), sometimes with blood in the urine, has been observed following administration into the bladder

Common: may affect up to 1 in 10 people
- Loss of water (dehydration)
- Impaired heart function (congestive heart failure). Symptoms may be:
    - Shortness of breath (dyspnoea)
    - Accumulation of fluid in the legs (oedema)
    - Enlargement of the liver
    - Accumulation of fluid in the abdominal cavity (ascites)
    - Accumulation of fluid in the lungs (pulmonary oedema)
    - Accumulation of fluid between thorax and lungs (pleural effusions)
    - Third heart sound (gallop rhythm)
- Local tissue skin toxicity, rash, itching, increased pigmentation of skin and nails, skin changes
- Redness along the vein (infusion site erythema)
- Bleeding
- Redness of the skin
- Chills
- Loss/lack of appetite
- Changes in heart function without any symptoms (asymptomatic drops in left ventricular ejection fraction)
- Life-threatening irregular heart beat (ventricular tachycardia), slow heart rate, defect of the heart's electrical conduction system (AV block, bundle-branch block)
- Bladder infection (bacterial cystitis), pain or burning when urinating, blood in urine, frequent urination have been observed following administration into the bladder.
- Ulcers in the gastrointestinal tract, Gastric erosions and lesions, gastrointestinal bleeding, Pain behind the breastbone, indigestion, and difficulty in swallowing due to inflammation in the oesophagus, pain or burning in the gastrointestinal tract, inflammation of the mucous membrane of the gastrointestinal tract and inside the mouth with a burning sensation and pain

Uncommon: may affect up to 1 in 100 people
- Certain types of blood cancer (acute lymphocytic leukaemia, acute myeloid leukaemia)
- Blood poisoning (sepsis), infection of the lungs (pneumonia)
- Feeling of weakness (asthenia)
- Skin reddening (erythema), hives
- Blockage in a blood vessel
- Swelling and pain in the legs or arms due to inflammation of a blood vessel, possibly including blood clotting
- Blood clots in the lungs which causes chest pain and breathlessness

Rare: may affect up to 1 in 1 000 people
- Sudden life-threatening allergic reaction. Symptoms include sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing, allergic reactions after administration of the medicine into the bladder
- Increased levels of uric acid in the blood
- Dizziness
- Toxic effects on the heart like abnormalities in ECG (electrocardiogram), different forms of irregular heart beat (arrhythmias) or heart muscle disease (cardiomyopathy)
- Lack of sperm in the semen

Not known: frequency cannot be estimated from the available data

- Life-threatening condition that occurs when the blood pressure is too low due to blood poisoning (septic shock)
- Life-threatening condition where the blood pressure is too low (shock)
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Inadequate oxygen supply of tissue may occur as a result of inhibition of blood-cell production in the bone marrow (myelosuppression)
- Occlusion of blood vessel by dislodged blood clot (thromboembolism)
- Thickening of the vein walls, local pain, severe cellulitis
- Increased colouring of the mucosa of the mouth
- Increased sensitivity to light (photosensitivity), increased sensitivity to irradiated skin (radiation-recall reaction)
- Severe damage of the tissue following leakage of the injection solution into the surrounding tissue
- Headache
- Pain

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 listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epimedac

Store in a refrigerator (2 °C – 8 °C).
Keep the vial in the outer carton in order to protect from light.

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

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 Epimedac contains
- The active substance is epirubicin hydrochloride.
- The other ingredients are sodium chloride, hydrochloric acid and water for injections.

1 ml of solution contains 2 mg epirubicin hydrochloride.

One 5 ml (10 ml, 25 ml, 50 ml, 100 ml) vial contains 10 mg (20 mg, 50 mg, 100 mg, 200 mg) epirubicin hydrochloride.

What Epimedac looks like and contents of the pack
Epimedac is a clear, red solution.
It is supplied in single vials.

Marketing Authorisation Holder and Manufacturer
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This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Denmark	Epirubicin medac 2 mg/ml injektionsvæske, opløsning
Finland	Epirubicin medac 2 mg/ml injektioneste, liuos
	Epirubicin medac 2 mg/ml injektionsvätska, lösning
Germany	Epimedac 2 mg/ml Injektionslösung
Norway	Epirubicin medac 2 mg/ml injeksjonsvæske, oppløsning
Poland	Epimedac 2 mg/ml roztwór do wstrzykiwań
Portugal	Epirrubicina medac 2 mg/ml solução injectável
Slovak Republic	Epimedac 2 mg/ml injekčný roztok
United Kingdom (Northern Ireland)	Epirubicin hydrochloride 2 mg/ml solution for injection

This leaflet was last revised in March 2023.

The following information is intended for healthcare professionals only:

Epimedac may be further diluted in glucose 50 mg/ml (5 %) solution or sodium chloride 9 mg/ml (0.9 %) solution and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.

The solution for injection contains no preservative and any unused portion of the vial should be disposed of immediately in accordance with local requirements.

Incompatibilities
Prolonged contact of the medicinal product with any solution of an alkaline pH (including sodium bicarbonate solutions) should be avoided; this will result in hydrolysis (degradation) of the active substance. Only the diluents detailed in the section below should be used.

A physical incompatibility of the medicinal product with heparin has been reported.

This medicinal product must not be mixed with other medicinal products except those mentioned in the section below.

In-use stability
Epimedac may be further diluted, under aseptic conditions, in glucose 50 mg/ml (5 %) solution or sodium chloride 9 mg/ml (0.9 %) solution and administered as an intravenous infusion. The chemical and physical in-use stability has been demonstrated for 48 hours at 25 ºC in the absence of light. However, from a microbiological point of view, the product 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 to 8 ºC, unless dilution has taken place in controlled and validated aseptic conditions.

Guidelines for the safe handling and disposal of antineoplastic agents
1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.

2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective disposable gloves, goggles, gown and mask should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 9 mg/ml (0.9 %) sodium chloride solution and consult a doctor.
5. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
6. Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.
8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc.) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.