Package leaflet: Information for the user

Epirubicin 2 mg/ml solution for injection

Epirubicin hydrochloride

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epirubicin is and what it is used for

Epirubicin is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy, Epirubicin is part of a group of medicines called antrhacyclines. These act upon cells that are actively growing, to slow or stop their growth and increase the chance that the cells die.

Epirubicin is used to treat a variety of cancers. The way in which it is used depends upon the type of cancer that is being treated.

When injected into the bloodstream, Epirubicin is used to treat cancers of the breast, stomach and lung as well as advanced ovarian cancer.

When injected into the bladder through a tube, Epirubicin is used to treat cancers of the bladder wall. It can also be used after other treatments for prevention of such cells from growing again.

2. What you need to know before you use Epirubicin

Do not use Epirubicin:
- if you are allergic to epirubicin hydrochloride or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other similar drugs (belonging to a group of drugs called anthracyclines, which among others include doxorubicin or daunorubicin)
- if you are allergic to drugs belonging to the group anthracenediones (including drugs used to treat cancer)
- if you are breast-feeding

<u>Epirubicin should not be injected into a vein (intravenous use) if you:</u>
- are aware **your blood counts are low**, caused by previous treatment with other anti-tumour drugs or by previous radiotherapy
- have been treated with other **chemotherapy** at maximum dose such as epirubicin and/or other anthracyclines (such as doxorubicin or daunorubicin), and anthracenediones, which can increase the risk of side effects

- suffer with or have suffered with **problems with your heart**
- suffer from an acute severe infection
- have severe liver problems

Epirubicin should not be injected into the bladder if:
- you suffer from urinary tract infection (including your kidneys, bladder and urethra)
- there are tumours which penetrate the bladder
- there are problems placing the tube into the bladder
- you have an inflammation of the bladder
- you have blood in the urine (hematuria)

Warnings and precautions
Talk to your doctor before using /…/:
- if you have some kidney or liver problems
- if you have had or you are due to have any vaccination.

You should inform your doctor before treatment as he/she needs to take special care.

Your doctor will also be making regular checks
- so that your blood cell counts will not be too low
- to control the levels of uric acid and other factors in the blood
- to see that your heart and liver are working normally
- if you have or are to have radiotherapy to the area around the heart.

You should inform your doctor in case you experience swelling and pain in your mouth or mucous membrane.

It is possible that the urine will have a red colour for one or two days after administration.

Children
There is a lack of data on safety and efficacy in children.

Other medicines and Epirubicin
Tell your doctor if you are taking, have recently taken or might take any other medicines, especially:
- Cimetidine (used to reduce the acid in the stomach).
- Trastuzumab (used to treat cancer).
- Paclitaxel and docetaxel (used in some cancers).
- Interferon alfa-2b (used in some cancers and lymphoma and for some yellow fever).
- Quinine (used for treatment of malaria and for leg cramps).
- Dexverapamil (used to treat some heart conditions).
- Medicines that may affect your heart, such as 5-fluorouracil, cyclophosphamide, cisplatin, taxanes (used to treat cancer) or calcium channel blockers (used to treat high blood pressure or some heart conditions).
- Medicines that may affect your liver.
- Live vaccines.
- Other medicines that may affect the bone marrow (such as other medicines to treat cancer, sulphonamide and cloramphenicol (antibacterial medicines), diphenylhydantoin (antiepileptic), amidopyrine derivatives (some medicines to treat e.g. pain and fever) and some antiviral medicines).
- Dexrazoxane (used to prevent chronic cumulative cardiotoxicity caused by epirubicin).

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 for advice before taking this medicine.

Pregnancy

Epirubicin may cause birth defects when used during pregnancy, it is important to tell your doctor if you are pregnant or if you become pregnant during treatment. You must not use Epirubicin during pregnancy unless clearly indicated by your doctor.

If you or your partner are being teated with Epirubicin, effective birth control to prevent pregnancy is advised. If pregnancy occurs during treatment or if you desire to have children after completion of therapy, genetic counsellation is recommended.

Breast-feeding
Epirubicin may be harmful to nursing infants, therefore women must stop breast-feeding before starting treatment with Epirubicin.

Fertility
There is a risk of sterility due to therapy with Epirubicin. Male patients should consider storage of sperm before treatment.

Epirubicin may cause absence of menstruation or premature menopause in premenopausal women.

Driving and using machines
Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of the ability to drive or use machines.

Epirubicin contains sodium
Epirubicin contains 3.54 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Epirubicin

Epirubicin will be given to you by a doctor or nurse, either into a vein or directly into your bladder. Your doctor will decide the correct dose and number of days treatment you receive, this will depend on the type of cancer you have, your health, height, weight, how well your liver is working and any other treatment you may receive.

By injection or infusion into a vein
Epirubicin may be given as an injection into a vein over 3-5 minutes. It may also be diluted before it is infused slowly, usually via a drip into a vein over 30 minutes.

By being put into the bladder
If the injection is given into the bladder, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much. The solution should be kept in your bladder for 1-2 hours after installation. You will need to turn occasionally to make sure all parts of the bladder are exposed to the drug.

Care should be taken to ensure that the contents of the bladder, when emptied, do not come into contact with the skin. In case of skin contact, thoroughly wash the affected area with soap and water but do not scrub.

Your doctor will regularly check your blood for any unwanted effects. To detect any possible heart damage your doctor will also monitor your heart for several weeks after the treatment.

If you receive more Epirubicin than you should:
It may affect your heart, lower your blood cell count and cause gastrointestinal toxic effects (mainly mucositis). You may notice sores in your mouth. However, as this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much. Please tell your doctor if you have any concerns.

4. Possible side effects

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

If any of the following side effects happen when epirubicin is given by infusion into a vein tell your doctor immediately, as these are very serious side effects. You may need urgent medical attention:
- redness, pain or swelling at the injection site; tissue damage may occur after accidental injection outside a vein
- symptoms of heart problems or blood clot in the lungs, such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin)
- severe allergic reaction, symptoms include faintness, skin rash, swelling of the face and difficulty in breathing or wheeze . In some cases collapse may occur.
- fever with an extreme elevation of body temperature greater than 41°C (hyperpyrexia).

If you experience any of the following tell your doctor as soon as possible:

Very common (may affect more than 1 in 10 people):
Bone marrow suppression (which leads to low blood cell count), hair loss (usually reversible), reduced growth of beard hair, red coloured urine for 1 to 2 days after being given the medicine.

Common (may affect up to1 in 10 people):
Severe loss of appetite leading to weight loss (anorexia), loss of fluid from the body (dehydration), feeling or being sick (nausea or vomiting), diarrhoea (which can result in dehydration), loss of appetite, abdominal pain, inflammation of the gullet (oesophagitis), high levels of pigments in the mouth, swelling and pain in your mouth, ulcers involving the lips and/or tongue and/or under the tongue, hot flushes, fever or infections, redness, pain or swelling at the injection site; tissue damage may occur after accidental injection outside a vein, allergic reactions or inflammation of the bladder (sometimes with bleeding) after injection of the medicine into the bladder.

Uncommon (may affect up to 1 in 100 people):
Low levels of blood platelets (thrombocytopenia) often causing unusual bruising or bleeding, headache, high levels of pigments in the skin and nails, skin redness, sensitivity of the skin to light (in case of radiotherapy), vein inflammation including blood clotting (thrombophlebitis).

Rare (may affect up to 1 in 1,000 people):
Leukaemia (cancer of the blood), severe, whole-body allergic reaction (anaphylaxis), hives (urticaria), increased blood levels of uric acid (hyperuricaemia) possibly leading to gout, fever and/or chills, dizziness, absence of menstrual periods (amenorrhea), lack of sperm, gout, changes in heart or liver function, feeling generally unwell, feeling of weakness.

Not known (frequency cannot be estimated from the available data)
Infection of the lungs (pneumonia), infection of the blood (sepsis), septic shock (severe complication of sepsis), bleeding and lack of oxygen in body tissues, redness and swelling of the eyes, shock, blockage of a blood vessel by a clot (e.g. in the lungs), skin rash, itching, skin changes, flushing (reddening of the skin), severe cellulitis, oral pain, burning sensation inside the mouth.

If epirubicin hydrochloride is injected directly into the bladder you may experience pain or difficulty when passing urine or frequent urge to urinate. Blood may also be seen in your urine.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.

Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epirubicin

Keep this medicine out of the sight and reach of children.

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

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.

Do not use this medicine if you notice any visible signs of deterioration.

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 Epirubicin contains

- The active substance is epirubicin hydrochloride, each millilitre of solution for injection contains 2 mg epirubicin hydrochloride.
- The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injection.

What Epirubicin looks like and contents of the pack

Epirubicin 2 mg/ml solution for injection is a clear red solution.

Pack sizes:
1 x 5 ml vial (10 mg/5 ml)
1 x 10 ml vial (20 mg/10 ml)
1 x 25 ml vial (50 mg/25 ml)
1 x 50 ml vial (100 mg/50 ml)
1 x 100 ml vial (200 mg/100 ml)

One 5 ml vial of Epirubicin 2 mg/ml solution for injection contains 10 mg epirubicin hydrochloride equivalent to 9.35 mg epirubicin.
One 10 ml vial of Epirubicin 2 mg/ml solution for injection contains 20 mg epirubicin hydrochloride equivalent to 18.7 mg epirubicin.
One 25 ml vial of Epirubicin 2 mg/ml solution for injection contains 50 mg epirubicin hydrochloride equivalent to 46.75 mg epirubicin.
One 50 ml vial of Epirubicin 2 mg/ml solution for injection contains 100 mg epirubicin hydrochloride equivalent to 93.5 mg epirubicin.
One 100 ml vial of Epirubicin 2 mg/ml solution for injection contains 200 mg epirubicin hydrochloride equivalent to 187 mg epirubicin.

Marketing Authorisation Holder

Actavis Group hf.
Reykjavíkurvegi 76-78
IS-220 Hafnarfjörður
Iceland

Manufacturer

S.C. Sindan Pharma S,R.L.
11 Ion Mihalache Blvd.
011171 Bucharest
Romania

Actavis Italy S.p.A.
Nerviano Plant
Viale Pasteur 10
20014 Nerviano (Milan)
Italy

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

Denmark:	Epirubicin Actavis
Austria:	Epirubicin Actavis 2 mg/ml Injektionslösung
Belgium:	Epirubicin Actavis Group 2 mg/mlOplossing voor injectie
Germany:	Epirubicin-Actavis 2 mg/ml Injektionslösung
Spain:	Epirubicina Actavis 2 mg/ml solución inyectable
Finland:	Epirubicin Actavis
Iceland:	Epirubicin Actavis
Italy:	Epirubicina cloridrato Actavis
Portugal:	Epirrubicina Actavis
UK:	Epirubicin Hydrochloride 2mg/ml solution for injection

This leaflet was last revised in {**May 2015**}.

Detailed information on this medicine is available on the web site of {MA/Agency}

The following information is intended for healthcare professionals only:

Epirubicin 2 mg/ml solution for injection
Instructions for use

ANTINEOPLASTIC AGENT

Incompatibilities
Prolonged contact with any solution of an alkaline pH (including bicarbonate containing solutions) should be avoided as it will result in hydrolysis of the drug. Only the diluents detailed in "Instructions for use" should be used.

Neither the injection nor any diluted solution should be mixed with any other drugs. A physical incompatibility with heparin has been reported.

Epirubicin should not be mixed with other drugs.

Instructions for use
Intravenous administration: It is advisable to administer Epirubicin via the tubing of a freely flowing intravenous infusion (0.9 % sodium chloride). To minimize the risk of thrombosis or perivenous

extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Intravesical administration: Epirubicin should be diluted in sterile water for injection or 0.9 % sterile saline solution before administration. Epirubicin should be instilled using a catheter and retained intravesically for 1-2 hours. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation,

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

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 0.9 % sodium chloride solution. Then seek medical evaluation by a physician.

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 product or waste material should be disposed of in accordance with local requirements.

Storage
Product as package for sale: Store in a refrigerator (2°C-8°C). Keep the vial in the outer carton in order to protect from light.

After first opening the container:
From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

After dilution of the solution for injection:
The product should be used immediately after first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

Please refer to the Summary of Product Characteristics (SPC) for further information about Epirubicin 2 mg/ml solution for injection.