**PACKAGE LEAFLET: INFORMATION FOR THE USER**
**Epirubicin hydrochloride 2 mg/ml, solution for injection**

**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 or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

**What is in this leaflet:**



## 1. What Epirubicin is and what it is used for

Epirubicin contains the active substance Epirubicin hydrochloride, referred to as "epirubicin" throughout this leaflet.

Epirubicin is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.
Epirubicin is used in the treatment of:
- Cancer of the breast
- Cancer of the stomach
- Cancer of the ovaries
- Cancer of the lung (small cell lung cancer)
- It is used either alone or in combination with other anti-cancer medicines

Epirubicin is also used intravesically to treat early (superficial) urinary bladder cancer and help prevent recurrence of bladder cancer after surgery.

## 2. What you need to know before you use Epirubicin

### Do not use Epirubicin:
- if you are allergic (hypersensitive) to epirubicin, similar medicines (called anthracyclines or anthracenediones - see below) or any of the other ingredients of Epirubicin hydrochloride 2 mg/ml, solution for injection (listed in section 6)
- if you have been treated with high doses of some other anticancer drugs including doxorubicin and daunorubicin which belong to the same group of drugs as epirubicin

(called anthracyclines and anthracenediones). They have similar side-effects (including those effects on the heart)
- if you have suffered or are currently suffering heart problems
- if you are breast-feeding
- if you have a low blood count. Your doctor will check this
- if you are suffering from severe liver impairment
- if you have an acute severe infection
- if you have pain and swelling of the lining of the mouth or digestive system (mucositis)

When administered intravesically (directly into the bladder), epirubicin solution for injection/intravesical use should not be used if:
- the cancer has penetrated the bladder wall
- you have an infection in your urinary tract
- you have pain or inflammation in your bladder
- your doctor has problems inserting a catheter (tube) into your bladder
- there is blood in your urine
- you have a large amount of urine left in your bladder after emptying it
- you have a contracted bladder

**Warnings and precautions**
**Talk to your doctor or pharmacist before using Epirubicin:**

- if you are elderly because of the higher risk of serious cardiovascular side effects. The way your heart is working will be studied before and after treatment with epirubicin
- if you have a history of heart problems or are suffering from heart problems. Tell your doctor as your epirubicin dose may need to be adjusted. Your doctor will check this regularly
- if you have been previously treated with anticancer drugs, or if you have received radiotherapy as the risk of cardiovascular side effects are greater. This can have an impact on the dosing of epirubicin
- if you have liver or kidney disease as this may increase the risk of side effects
- if you suffer from infections or bleeding. Epirubicin may affect the bone marrow. The number of white blood cells in your blood will be reduced, making you more susceptible to infections (leukopenia). Bleeding can occur more easily (thrombocytopenia).These side effects are transient. Reduction of white blood cell count is highest 10-14 days after administration and usually return to normal 21 days after administration
- if you have recently had or plan to have a vaccination
- if you have severe inflammation or sores in your mouth
- if you have received or will receive radiotherapy on the chest area
- if you notice a burning sensation of discomfort redness, pain or swelling close to or at the place of injection during the infusion (possible leakage of epirubicin into the surrounding tissue). Tell your doctor immediately.

During treatment your doctor will be making regular checks of your:

- **Blood** - to check for low blood cell counts that may need treatment

- **Heart function** - heart damage can occur when high doses of epirubicin are given. This may not be detected for several weeks, so regular tests may be required during this period
- **Liver** – using blood tests to check that this medicine is not affecting the way it functions in a harmful way
- **Blood uric acid levels** – epirubicin may increase uric acid levels in the blood which might cause gout. Another medicine may be given if your uric acid levels are too high

**Other medicines and Epirubicin:**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines:

- other medicines that may affect the bone marrow for example, other cancer treatments, sulphonamide, chloramphenicol (used to treat infection), diphenylhydantoin (used to treat epilepsy), amidopyrine-derivative (used to relieve pain), antiretroviral agents (used to treat HIV infection) may alter the formation of blood cells
- paclitaxel and docetaxel (drugs used in some cancers)
- dexverapamil (a drug used to treat some heart conditions), when used in combination with epirubicin can have a negative effect on bone marrow
- interferon alpha-2b (a drug used in some cancers and lymphomas and for some forms of hepatitis)
- quinine (drug used for treatment of malaria and for leg cramps), can increase the distribution of epirubicin in the body, which may have a negative effects on the red blood cells
- dexrazoxane (a drug sometimes used with doxorubicin to reduce the risk of heart problems), the period which epirubicin is present in the body can be reduced, which may lead to the effect of epirubicin being reduced
- cimetidine (a medicine that reduces stomach acid), can make the effects of epirubicin stronger, which can lead to increased side effects.
- products that cause heart failure
- products that affect liver function, the metabolism of epirubicin may be affected, which may mean that efficacy is reduced, or that undesirable effects are increased
- live and attenuated vaccines, the response to vaccines may be reduced and leave you susceptible to infection

**Epirubicin with food and drink**
If you being given this medicine directly into your bladder (intravesical administration), you should not drink any fluid for 12 hours prior to dosing to avoid undue dilution with urine
**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.

<u>Pregnancy</u>
Epirubicin may cause births defects, so it is important to tell your doctor if you think you are pregnant. You must not use epirubicin during pregnancy unless clearly indicated by your doctor. Avoid becoming pregnant while you or your partner is taking epirubicin and for 6

months after treatment. If pregnancy occurs during treatment with Epirubicin, genetic counselling is recommended.

Lactation
You must discontinue breast-feeding before and during therapy with epirubicin.

Fertility
If you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female.

Epirubicin may cause premature menopause in premenopausal women.

Men who wish to father children in the future should seek advice about freezing sperm before treatment with epirubicin is started.

**Driving and using machines**
No studies on the effects on the ability to drive and use machines have been performed with epirubicin.

**3. How to use Epirubicin**

Epirubicin will only be given to you under supervision of a doctor specialised in this type of treatment. Before and during treatment with epirubicin 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 Epirubicin.

When given by injection or infusion into a vein:

Each dose of epirubicin is based on your body surface area. This is calculated from your height and weight. The dose of epirubicin given to you will also depend on the type of cancer you have, your health, how well your liver or kidney is working and any other medicines you may be taking.

When given as a single agent, the usual dose is 60-90 mg/m$^2$ body surface area. Higher dosages (100-120 mg/m$^2$ body surface area) may be given to you if you suffer from breast cancer.

Dosage will be reduced or the following dose could be delayed if you have a low level of white blood cells in your body, if you are elderly, if you have liver problems, or if the drug is used in combination with other anticancer drugs.

Epirubicin may be given as an injection into a vein over 3-5 minutes. It may also be diluted with glucose (sugar solution) or sodium chloride (salt water) before it is infused slowly, usually via a drip into a vein over 30 minutes. Usually it will be given to you every 3 (or 4) weeks.

The needle must remain in the vein while epirubicin is being given. If the needle comes out or becomes loose, or the solution is going into the tissue outside the vein (you may feel discomfort or pain) - tell the doctor or nurse immediately.

**When given directly into the bladder (intravesical administration):**
The medicine may be given directly into the bladder using a catheter. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much.

The dose will depend upon the type of bladder cancer.

The solution should be kept in your bladder for 1-2 hours after instillation. You will be rotated occasionally to ensure even exposure of all parts of the bladder 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.

**If you received more Epirubicin than you should:**
As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too much, however, tell your doctor or pharmacist if you have any concerns.

**If you forgot to take Epirubicin**
Epirubicin needs to be given on a fixed schedule. Be sure to keep all appointments. If you miss a dose, you should discuss this with your doctor. Your doctor will decide when you should be given your next dose of epirubicin.

**If you stop taking Epirubicin**
Stopping your treatment with epirubicin may stop the effect on tumour growth. Do not stop treatment with epirubicin unless you have discussed this with your doctor.

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

**4. Possible side effects**

Like all medicines, epirubicin 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:

- redness, pain or swelling at the injection site; tissue damage may occur after accidental injection outside a vein
- symptoms of heart problems 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 wheezing. In some cases collapse may occur

You may need urgent medical attention.

More than 10% of patients may be expected to develop side effects. The most common side effects are decreased production of blood cells (myelosuppression), side effects in the gastro-intestinal system, loss of appetite (anorexia), hair loss (alopecia) and infection.

The following side-effects are possible for epirubicin and you should tell your doctor as soon as possible if they occur:

*Very common (estimated frequency is more than 1 person out of 10):*

- inhibition of blood cell production in the bone marrow (myelosuppression)
- decreased number of white blood cells (leucocytopenia)
- decreased number of a special form of white blood cells (granulocytopenia and neutropenia)
- neutropenia accompanied by fever (febrile neutropenia)
- decrease in red blood cells (anaemia)
- decreased number of platelets (thrombocytopenia)
- bleeding (haemorrhage) and tissue hypoxia (inadequate oxygen supply) as a result of myelosuppression
- hair loss (alopecia) normally reversible
- lack of beard growth in males
- red colouration of urine for up to two days after treatment. This is normal and nothing to worry about

*Common side effects (estimated frequency is less than 1 person out of 10 but more than 1 out of 100):*

- infection
- loss of appetite
- feeling very dry and thirsty (dehydration)
- hot flashes
- heartburn, nausea (feeling sick), vomiting (being sick) or diarrhoea
- pain, redness, burning or stinging sensation at injection site
- abdominal pain
- inflammation of the oesophagus (oesophagitis)
- inflammation of a mucous membrane (mucositis)
- inflammation of the mucosa of the mouth with areas of painful erosions, ulceration and bleeding (stomatitis)
- increased pigmentation (hyperpigmentation) of the oral mucosa
- bladder inflammation with pain when passing urine (chemical cystitis), sometimes with blood in the urine (haemorrhagic) following administration into the bladder
- inflammation of the walls of a vein (phlebitis)
- thickening of the vein walls (phlebosclerosis)
- pain and bleeding in the mouth

*Uncommon side effects (estimated frequency is less than 1 person out of 100 but more than 1 out of 1000):*

- headache
- bruising and a tendency to bleed (due to shortage of blood platelets (thrombocytopenia)). It is important to seek medical advice if this happens.

- vein inflammation (swelling, redness & pain) related to a blood clot (thrombophlebitis)
- increased pigmentation (hyperpigmentation) of skin and nails
- sensitivity to light or hypersensitivity in the case of radiotherapy

*Rare side effects (estimated frequency is less than 1 person out of 1000 but more than 1 out of 10, 000):*

- when given in combination with other anti-cancer drugs, some patients have developed a rare leukaemia (cancer of white blood cells) after completing treatment
- severe hypersensitivity (anaphylaxis)
- increased levels of uric acid in the blood (hyperuricaemia), which may cause gout
- dizziness
- gasping for air, shortness of breath, swelling of abdomen, legs or ankles, fluid in lungs (signs of congestive heart failure)
- ECG abnormalities, irregular heartbeat, heart muscle disease
- Rashes on the skin with the formation of small dents (hives) or with severe itching (pruritis)
- absence of menstruation (amenorrhea)
- lack of sperm in the semen (azoospermia)
- feeling of discomfort (malaise)
- fever, chills
- increased levels of liver enzymes (transaminases)
- accumulation of fluid (oedema)
- enlargement of the liver
- accumulation of fluid in the abdominal cavity (ascites)
- lung oedema
- accumulation of fluid between thorax and lung (pleural effusions)

*Not known: frequency cannot be estimated from the available data:*

- blood infection
- pneumonia
- shock
- inflammation to the eye (conjunctivitis and keratitis)
- blood clots, including a clot in the lungs which causes chest pain and breathlessness

**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: Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

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

**5. How to store Epirubicin**

Keep the medicinal product out of the sight and reach of children.

Do not use Epirubicin after the expiry date which is printed on the label and carton after EXP. The expiry date refers to the last day on that month**.**

Shelf Life before opening: 2 years
Store in a refrigerator (2-8°C).
Keep the vial in the outer carton in order to protect from light.

From a microbiological point of view, the product upon opening should be used immediately and the remains discarded.

From a chemical and physical point of view, the product should be used immediately after dilution. Any unused portion must be discarded after use.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. Contents of the pack and other information**

What Epirubicin contains

- The active substance is 2 mg/ml epirubicin hydrochloride.
- The other ingredients are sodium chloride, water for injection and hydrochloric acid used as a pH adjuster.

**What Epirubicin looks like and contents of the pack**
A clear red solution for injection.
This medicinal product is available in glass packaging with a rubber stopper, called vials, with 10 mg (5 ml), 20mg (10 ml),50 mg (25 ml), 100 mg (50 ml) and 200 mg (100 ml) epirubicin hydrochloride.

Pack sizes:
Glass vials containing 5ml, 10ml, 25ml, 50ml and 100ml supplied in the following pack sizes:
1 x 5 ml,1 x 10 ml, 1 x 25 ml, 1 x 50 ml, 1 x100 ml.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Seacross Pharmaceuticals Ltd.
Bedford Business Centre
61 - 63 St. Peter’s Street
Bedford MK40 2PR
United Kingdom

**Manufacturer**
Genepharm S.A.
18th km Marathonos Avenue, 153 51 Pallini Attikis

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**This leaflet was last revised in March 2016**

The following information is intended for medical or healthcare professionals only:
**Epirubicin hydrochloride 2 mg/ml, solution for injection**

| For Intravenous and Intravesical Administration |
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**Incompatibilities**

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

**Dilution Instructions**

The injection may be given via the tubing of a free-running intravenous sodium chloride 0.9% infusion. Where the injection is to be administered after dilution, the following instructions should be followed.
Epirubicin solution for injection may be diluted under aseptic conditions in glucose 5% or sodium chloride 0.9% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.
The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

| Dose Epirubicin required | Volume of 2 mg/ml epirubicin injection | Volume of diluent sterile sodium chloride | Total volume for bladder instillation |
|---|---|---|---|
| 30 mg | 15 ml | 35 ml | 50 ml |
| 50 mg | 25 ml | 25 ml | 50 ml |
| 80 mg | 40 ml | 10 ml | 50 ml |

**Safe Handling**

This is a cytotoxic product, please follow your local policy guidelines for instruction on the safe handling /disposal of cytotoxics.

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, 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**

Store at 2-8 $^{o}$C.
Keep vial in the outer carton.