Package leaflet: Information for the user
Epirubicin "Ebewe" 2mg/ml –solution for injection or infusion
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 or nurse.
- This medicine has been prescribed for you only. Do not pass it onto others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or nurse. 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 belongs to the therapeutic group of antineoplastic agents (anti-cancer agent).
It is used either alone or in combination with other anti-cancer medicines.
Epirubicin is used to treat malignant neoplastic diseases:
It has shown efficacy in breast cancer.
There is some evidence that indicate objective response in non-Hodgkin's lymphoma, breast-, ovarian, gastric-, lung-cancer and leukemias.
Intravesical administration (where the medicine is put directly into the bladder) of Epirubicin has been shown to be beneficial in superficial bladder cancer.

2. What you need to know before you use Epirubicin

You will not be given Epirubicin if you:

- are hypersensitivity (severe allergy) to the active substance or any of the ingredients (please see section 6 for further information on the ingredients)
- are pregnant or breast-feeding
- have fewer blood cells than normal (your doctor will check this) induced by previous treatment with epirubicin, other antitumour agents as these medicines can increase the risk of side effects
- you have already been treated with maximal cumulative doses of other anti-cancer medicines belonging to the same therapeutic group (have a current or previous history of sever hear trouble in the past, or are presently receiving treatment for this.

- Sever liver problems
- Severe infections
- Severe heart problems such as heart failure, abnormal heart rhythms
- You will not be given intravesical epirubicin if you have a urine infection, blood in the urine, bladder inflammation, certain types of bladder tumour, or a blockage that makes it hard to insert a catheter

Warnings and precautions
Talk to your doctor or nurse before starting treatment so your doctor can determine a baseline for a number of laboratory tests which may be required to be monitored during treatment (e.g. blood cell count, blood uric acid level, heart tests, your liver function).

Tell your doctor if:
- your liver or kidneys are not working properly
- you have had or you are due to have any vaccination.

This will help your doctor decide if this medicine is suitable for you.

Epirubicin "EBEWE" may impart a red colour to the urine for 1-2 days after administration

Taking other medicines and Epirubicin
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines even those not prescribed, particularly the following:

- **Cimetidine** (a drug used to reduce the acid in your stomach and treat ulcers and heartburn)
  Cimetidine can make the effects of epirubicin stronger
- **Calcium channel blockers** (medicines for the heart)
- **Quinine** (antimalaria drug)
- **Antibiotics** such as sulphonamide and chloramphenicol
- **Antiretroviral** (drugs used to treat infection by HIV)
- **Diphenylhydantoin** (a drug used to treat epilepsy)
- **Painkillers** such as amidopyrine derivate.
- **Trastuzamab** therapy for treatment of cancer
- **Dexrazoxane** (used to prevent chronic cumulative cardiotoxicity caused by
- epirubicin).
- **Live vaccines**
- **Interferon**

Epirubicin should not be
- diluted in alkaline infusion solutions (e.g. hydrogen carbonate solutions)
- used with other medicines except in-combination with other anti-cancer medicines.
- used with heparin (due to chemical incompatibility)
- used with other preparations except Sodium Chloride Intravenous Infusion 0.9% w/v, Glucose Intravenous Infusion 5% w/v or Sodium Chloride and Glucose Intravenous Infusion

Pregnancy, breast-feeding and fertility

Pregnancy

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.

Women of child-bearing age should avoid becoming pregnant while you or your partner is being treated with this medicine. If you are sexually active, you are advised to use effective birth control to prevent pregnancy during treatment, whether you are male or female. It may cause birth defects, so it is important to tell your doctor if you think you are pregnant**.**

Breast feeding

This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding. You should stop breast feeding before starting treatment with this medicine as some of the drug may get into your milk and possibly harm your child.

Ask your doctor or pharmacist for advice before taking any medicine whilst breast feeding.

Driving and using machines

There are no special precautions, as long as you feel fully recovered following your hospital treatment and you have discussed this with your doctor.

Important information about some of the ingredients of Epirubicin

This medicinal product contains the following quantities of sodium per vial:

• 5 ml solution contains 0.77 mmol (17.70 mg) sodium.
• 25 ml solution contains 3.85 mmol (88.52 mg) sodium,
• 50 ml solution contains 7.70 mmol (177.02 mg) sodium and
• 100 ml solution contains 15.40 mmol (354.05 mg) sodium

3. How Epirubicin is given to you

If you are prescribed epirubicin it will only be given to you by doctors or nurses experienced in giving chemotherapy

Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

This medicine will normally be given to you by a doctor or a nurse through a drip (infusion) into a vein. Your doctor will decide what dose to give and the number of days' treatment you will receive depending on your condition.

The dose is decided by taking into account the condition you have, your height and weight. From your height and weight the doctor will work out your body surface area, and it is this that your dose is calculated from.

Epirubicin can also be put directly into the bladder to treat bladder cancer, or to help prevent it returning. The dose depends on the type of bladder cancer you have. When this medicine is injected directly into the bladder, you will be instructed not to drink any fluid for 12 hours before treatment to avoid dilution of the medicine with urine in your bladder. While one course of treatment may sometimes be enough, more often your doctor will advise further courses in three or four weeks' time. It may take several courses before your illness is under control and you feel better.

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. High doses can worsen side effects like sores in the mouth or may decrease the number of white blood cells (which fight infection) and platelets (these help the blood to clot) in the blood. Should this happen, you may need antibiotics or blood transfusions. Mouth ulcers can be treated to make them less uncomfortable as they heal.

If you missed a dose of 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.

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

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

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

Please contact your doctor or nurse immediately if you notice any of the following side effects. Although they are rare **(these may affect between 1 in 10,000 and 1 in 1,000 people)**,

- faintness, skin rash, itching, fever, chills, swelling of the face and difficulty in breathing of wheeze. In some cases collapse may occur.

These are very serious side effects of an allergic reaction. You may need urgent medical attention.

Very common possible side effects (these may affect at least 1 in 10 people)

- White blood cell counts (which fight infection) can drop, which increases the chance of infections and fever.
- A low red blood cell count (anaemia) that can leave you feeling tired and lethargic.
- Hair loss - may be quite severe. Beard growth may stop in men. Hair normally regrows when your treatment course ends.
- Red discolouration of urine (which is normal and related to the colour of the medicine). You should inform your doctor if it does not stop in a few days or you think there is blood in your urine.

Common possible side effects (these may affect between 1 in 100 and 1 in 10 people)

- Infections.
- Loss of appetite.
- Dehydration.

- Hot flushes.
- Soreness or ulcers in the mouth, which may not appear until 3-10 days after treatment.
- Heartburn, nausea (feeling sick), vomiting (being sick) or diarrhoea.
- Pain, redness, burning or stinging sensation at injection site.
- Irritation of the bladder or damage to the bladder wall (called necrosis).

Uncommon possible side effects (these may affect between 1 in 1,000 and 1 in 100 people)

- Platelets (cells that help the blood to clot) can be affected which could make you bruise or bleed more easily. It is important to seek medical advice if this happens.
- Swelling, redness, leg pain, which can be associated with blood clots.

Rare possible side effects (these may affect between 1 in 10,000 and 1 in 1,000 people)

- When given in combination with other anti-cancer drugs, some patients have developed a rare leukaemia (cancer of white blood cells) after completing treatment.
- Tiredness, weakness and feeling cold.
- Low sperm count.
- Absence of menstruation.
- 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.
- Changes in liver enzyme levels.
- Increase uric acid levels in the blood which might cause gout.

Not known (cannot be estimated from the available data)

- Blood infection.
- Pneumonia.
- Internal bleeding.
- Inflammation to the eye (conjunctivitis and keratitis).
- Shock.
- Discolouration of skin and nails.
- Sensitive to light.
- Blood clots, including a clot in the lungs which causes chest pain and breathlessness.
- Skin infection
- hardening of the veins
- tissue death around the vein

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

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.

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

The product should be store between 2- 8ºC
Storage of the medicinal product at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after 2 to a maximum of 4 hours equilibration at controlled room temperature (15° to 25°C)

Unopened shelf life of 2 years.

The product should be used immediately after opening. Remove solution from vial immediately before use.
From a microbiological point of view, the product should be used immediately after dilution.
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°C, unless dilution has taken place in controlled and validated aseptic conditions. Tests of the diluted solution up to 96 hours at 2-8°C and room temperature (20-25°C) show no significant changes without protection from light.

Do not use this medicine if you notice the solution is not clear red or the vial is damaged.

Do not throw away any medicines via wastewater or household waste.
Handle according to guidelines for cytotoxics.

6. Contents of the pack and other information

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

Each ml of solution contains 2 mg of epirubicin hydrochloride.
5ml vial: each vial contains 10 mg epirubicin hydrochloride.
25ml vial: each vial contains 50 mg epirubicin hydrochloride.
50ml vial: each vial contains 100 mg epirubicin hydrochloride.
100ml vial: each vial contains 200 mg epirubicin hydrochloride.

What epirubicin looks like and contents of the pack

The solution for injection or infusion is a clear, red solution.
Vials are clear glass with rubber stoppers and crimp cap of a nominal capacity of 5ml, 25ml, 50ml, and 100ml

Not all presentations may be marketed.

Marketing Authorisation Holder:
Fannin Limited
Fannin House, South County Business Park,
Leopardstown, Dublin 18
Manufacturer and site of batch release
EBEWE Pharma, Mondseestrasse 11, 4866 Unterach, Austria

This leaflet was last approved in December 2014

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling and disposal
Recommended infusion solutions are Sodium Chloride Intravenous Infusion 0.9% w/v, Glucose Intravenous Infusion 5% w/v or Sodium Chloride and Glucose Intravenous Infusion
The following protective recommendations are given due to the toxic nature of this substance.
• personnel should be trained in good technique for reconstitution and handling.
• pregnant staff should be excluded from working with this drug.
• personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
• a designated area should be defined for reconstitution (preferably under a laminar flow system).

The work surface should be protected by disposable, plastic-backed, absorbent paper.
• all items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.

Epirubicin is not absorbed to or affected by PVC, PE or clear neutral glass.
Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.
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 indicated previously.
Handle according to the guidelines for cytostatics.

Extravasation
It is advisable to give the drug via the tubing of a freely-running i.v. saline infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug

extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of epirubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Infusion preparations are to be prepared either with 0.9 % sodium chloride or with 5 % glucose.

Infusion preparations are to be prepared either with 0.9 % sodium chloride or with 5 % glucose.

When Epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body area; the drug should be injected i.v. over 3-5 minutes and depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

When epirubicin is given in combination with other cytotoxic drugs the dose of epirubicin should be adjusted to the toxicity of the other combination partners. Since the major route of elimination of Epirubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4-3 mg/100 ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Intravesical administration: As a guide 50 mg/50 ml Epirubicin diluted with saline or distilled sterile water. The solution should be retained intravesically for one hour. In case of local toxicity (chemical cystitis) a dose reduction is advised (30 mg/50 ml).

Incompatibilities
Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.
It cannot be recommended to mix the product with other medicinal products.