Package leaflet: Information for the user

Epirubicin 2 mg/ml solution for injection or infusion

epirubicin hydrochloride

Read all of this leaflet carefully before you start being 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 Epirubicin is and what it is used for

This medicine contains the active substance epirubicin (as hydrochloride), which belongs to the group of cytostatics (medicines to fight cancer).

Epirubicin makes sure that cancer cells cannot grow any more, which eventually kills them.

Epirubicin is administered for the treatment of:
- breast cancer;
- stomach cancer;

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

Epirubicin is often used together with other anti-cancer medicines (in so-called polychemotherapy schedules).

2. What you need to know before being given Epirubicin

You must not be given Epirubicin
- if you are **allergic** to epirubicin, similar medicines (called anthracyclines or anthracenediones, see below) or any of the other ingredients of this medicine (listed in section 6);
- if you have been **treated before with high doses** of some other anti-cancer medicines including doxorubicin and daunorubicin which belong to the same group of drugs as epirubicin (called *anthracyclines).* They have similar side effects (including those effects on the heart);
- if you suffered or currently have **severe heart problems***;*
- if you have a **low blood count***;*
- if you have a **severe liver function disorder***;*
- if you suffer from an **acute severe infection**.

You must discontinue **breast feeding** before being given Epirubicin .

When administered intravesically (directly into the bladder), Epirubicin should not be given if:
- the cancer has penetrated the bladder wall;
- you have an infection in your urine tract;
- you have pain or inflammation in your bladder;
- your doctor has problems inserting a catheter (tube) into your bladder;
- there is a large volume of urine left in your bladder after you attempt to empty it;
- if your urine contains blood;
- if you have a contracted bladder.

Warnings and precautions
Talk to your doctor or nurse before being given Epirubicin :
- if you are **elderly** because of the higher risk of severe cardiac side effects. Your cardiac function will be checked before and after the treatment with epirubicin.
- if you have had **problems with your heart** in the past or if you are currently experiencing such problems. You should inform your doctor. The dose of epirubicin will have to be adjusted.
- if you have a **liver or kidney** disorder. This may cause an increase in side effects.
- if you **desire to have children** (see "Pregnancy, breast-feeding and fertility").
- if you have received or are receiving radiotherapy to the chest area.

Tell your doctor if any of the above mentioned warnings are applicable to you, or has been applicable to you in the past.

During treatment
Talk to your doctor or nurse during treatment with Epirubicin :
- if you suffer from **infections or bleedings**. Epirubicin may affect the bone marrow. The number of white blood cells in your blood will be reduced, which makes you more susceptible to infections (leucopoenia). Bleedings can occur more easily (thrombocytopenia). These side effects are temporary in nature. The reduction of the number of white blood cells is greatest 10-14 days after the administration and usually returns to normal 21 days after the administration.
- if you are experiencing **severe inflammation or ulcers** in your mouth.
- if you get a **burning feeling** at the site of the administration. This could indicate that

epirubicin is leaking outside the blood vessel. Contact your doctor immediately about this.

Your doctor will do regular tests:
- to check the level of uric acid in your blood.
- to ensure the number of cells in your blood does not drop too low.
- to check your kidney, liver and heart function and if needed the dose will be adjusted.

Other medicines and Epirubicin

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

Epirubicin must not be given:

- if you have been **treated before with high doses** of some other anti-cancer medicines including doxorubicin and daunorubicin which belong to the same group of drugs as epirubicin (called anthracyclines) (see section 2 "You must not be given Epirubicin ").
- if you are taking **cimetidine** (a medicine to reduce the acid in your stomach). You must stop taking cimetidine during treatment with Epirubicin as the amount of epirubicin in the blood is increased, which could lead to an increase of the side effects.

Special care is required for:

- standard doses of anthracyclines (for instance the anti-cancer medicines **mitomycin-C, dacarbazine, dactinomycin**), or other medicines that may affect the heart (for instance the anti-cancer medicines **5-fluorouracil, cyclophosphaminde, cisplatin, taxanes**) or **calcium channel blockers** (used to treat high blood pressure or some heart conditions).
- The harmfulness to the heart can increase if these medicines are used before or with Epirubicin. Extra monitoring of the heart is then necessary.if you have been given **trastuzumab** (a medicine used to treat certain cancers like breast cancer)
- **rifampicin** (a medicine used for the treatment of tuberculosis) and **barbiturates** (medicines that are used for insomnia or epilepsy, such as for instance phenobarbital); these medicines decrease the amount of epirubicin in the blood, which could lead to a reduced effect of epirubicin.
- **paclitaxel** and **docetaxel** (medicines that are used for some cancers); when paclitaxel is administered before epirubicin or docetaxel is administered immediately after epirubicin, the amount of epirubicin in the blood is increased, which could lead to an increase of the side effects.
- **dexverapamil** (a medicine that is used to treat some cardiac disorders); when used together with epirubicin it may have a negative effect on bone marrow.
- **interferon alpha-2b** (a medicine used in some cancers and lymphomas and some forms of hepatitis).
- **quinine** (a medicine used for treatment of malaria and for leg cramps); quinine may speed up the distribution of epirubicin into the body, which may have a negative effect on the red blood cells.
- **dexrazoxane** (a medicine sometimes used with doxorubicin to reduce the risk of heart problems); the time that epirubicin is present in the body may be decreased, which could lead to decreased effect of epirubicin.
- previous or concomitant treatment with other medicines which influence the bone marrow (for instance **other medicines to treat cancer, sulfonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, medicines to treat HIV/AIDS**)*;* the formation of blood cells can be disturbed.
- **medicines that cause heart failure** (speak to your doctor if you are not sure).
- **medicines that influence the liver function** (speak to your doctor if you are not sure); the degradation of epirubicin by the liver may be influenced, which may cause a reduced effect of epirubicin or an increase of the side effects.
- **live vaccines;** there is risk of fatal disease therefore this combination is not recommended. Tell your doctor if you have recently been given or want to be given any **vaccination**.
- **ciclosporin** (a medicine that suppresses the immune system); the immune system may be suppressed too much.

Epirubicin can increase the effect of radiation and even after quite some time after the radiation it can cause serious side effects in the irradiated area. Tell your doctor if you have previously had or are scheduled to have radiotherapy.

Epirubicin with drink
You should not drink within 12 hours before application when epirubicin will be administered in the bladder.

Pregnancy, breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist before being given this medicine.

Pregnancy
Medicines to fight cancer are only administered during pregnancy in extreme cases. The benefits for the mother must be weighed against the possible danger to the unborn child. In animal studies epirubicin proved to be harmful to the unborn child and can cause deformities. Both men and women should use good contraceptive measures (pill, condom) both during and for 6 months after the use of this medicine to prevent pregnancy.

You should also prevent pregnancy if your partner is treated with epirubicin.

If pregnancy occurs during treatment with epirubicin, genetic counselling is recommended.

Breast-feeding
It is not known whether epirubicin is excreted in the breast milk. You must **discontinue breast-feeding** during treatment with Epirubicin .

Fertility
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
Because many people get very nauseous or have to vomit during the treatment, driving and using machines is not recommended.

Epirubicin contains sodium
This medicine contains 3.5 mg sodium per ml solution for injection/infusion. To be taken into consideration by patients on a controlled sodium diet.

3. How Epirubicin is given

Epirubicin will only be given to you under supervision of a doctor specialised in this type of treatment. You should check with your doctor or pharmacist if you are not sure.

The dose you are administered will depend on the type of cancer you have, your health, your age, how well your liver functions and other medicines you are taking.

The recommended dose
Depending on your general health and possible previous treatments the dose schedule is determined, whereby your length and your weight are taken into account. The amounts in the dose schedule are expressed in numbers of milligrams per square metre of body surface area.
This medicine will be administered as

- an injection in a vein for 3 - 5 minutes

or

- an infusion in a vein for a maximum of 30 minutes.

If only epirubicin hydrochloride is administered, so without other cancer medicines, the recommended dose is **60-90 mg/m²** of body surface area. This dose is administered as a single dose or distributed over 2-3 consecutive days. This is repeated every 21 days. In combination with other cancer medicines the dose is reduced.

The administration occurs via a catheter or side line of a free running infusion of a sodium chloride or glucose (sugar solution).

Higher doses are used for the treatment of

- might be given for the treatment breast cancer: **100 - 120 mg/m²** of body surface area.

Administration via the bladder (intravesical administration)
The product can be given directly into the bladder (for the treatment of bladder cancer) by means of a catheter. If this method is used, you **must not drink any liquids for 12 hours** before the treatment, so your urine will not dilute the medicine too much. The dissolved medicine should be kept in your bladder for **1-2 hours** after it has been administered. You will have to change your position occasionally to make sure the medicine reaches all parts of your bladder.

When you empty your bladder after the medicine has been given, make sure that your urine does not get in contact with your skin. In case contact does take place, thoroughly wash the site of contact with water and soap but do not scrub.

While epirubicin is being administered to you your doctor will perform blood tests. This is to measure the effect of the medicine. Your doctor will also perform tests to see how your heart functions. Both blood test and heart function tests are done before and during treatment with

epirubicin.

If you notice that Epirubicin is too strong or too weak, consult your doctor or pharmacist.

If more Epirubicin was administered than should have been
Because this medicine is administered by medical personnel the risk of an overdose is unlikely. Immediately contact your doctor if you suspect that too much Epirubicin has been administered.

If you forget to use Epirubicin
Because this medicine is administered by medical personnel it is unlikely that a dose is missed.
You should check with your doctor if you are not sure.

If you stop using Epirubicin
Consult your doctor.

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.

If you notice any of the following side effects, tell your doctor straight away as you may need urgent medical attention or hospitalisation:

Very common: may affect more than 1 in 10 people
- Bone marrow depression is an abnormality in the blood, which means that fewer new blood cells are produced (resulting in a shortage of white blood cells, red blood cells, platelets; reduced number of a type of white blood cell (neutrophilic granulocytes) with fever), and which involves an increased sensitivity to infections. Your blood must be checked regularly.

Uncommon: may affect up to 1 in 100 people
- Bruising and a tendency to bleed (due to shortage of platelets (thrombocytopenia)).

Rare: may affect up to 1 in 1,000 people
- Severe and immediate allergic reaction (anaphylactic/anaphylactoid reaction) with or without shock including faintness, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, skin rash and itching; fever and chills.
- Risk of a reduced effect of the heart with as a result congestion of the blood (congestive heart failure), heart failure (short of breath; accumulation of fluid in the whole body (oedema), enlargement of the liver, accumulation of fluid in the abdomen (ascites), accumulation of fluid in or around the lungs (pulmonary oedema, pleural effusions), abnormal rhythm of the heart (gallop rhythm) cardiotoxicity (e.g. ECG abnormalities, arrhythmias, heart muscle disease (cardiomyopathy)).
- When epirubicin is used at the same time with certain anti-cancer medicines (so-called DNA-damaging antineoplastic substances) can in rare cases lead to certain forms of

cancer of the blood (secondary acute myeloid leukaemia (AML) with or without preleucaemic phase). These certain forms of cancer of the blood can only be observed after 1-3 years.
- Extremely high fever.

Not known: frequency cannot be estimated from the available data
- Blood poisoning (sepsis) (with symptoms such as fever, chills and shivering, a fast heartbeat, fast breathing) and shock as a result of blood poisoning sometimes with a dangerous drop in blood pressure with symptoms like cold skin and increased heart beat.
- serious lungs infection with fever, chills, shortness of breath, cough, phlegm and occasionally blood (pneumonia).
- Bleeding (haemorrhage), shortage of oxygen in tissue.
- Inflammation of the cornea (keratitis).
- Shock with symptoms such as a dangerous decrease in blood pressure which may be life-threatening; rapid shallow breathing, cold clammy skin, dizziness, weakness, fainting and a rapid weak pulse.
- Blockage of a blood vessel by a blood clot formed elsewhere in the body (thromboembolism), including blood clot formation in the lungs (pulmonary emboli, in very rare cases this resulted in death). Symptoms can include sudden severe headache, loss of vision, loss of coordination, slurred speech, shortness of breath, chest pain, numbness heat or swelling in the arms and legs.
- Swollen, red area of skin that feels hot and tender/painful that can spread rapidly to other parts of the body (severe cellulitis).
- Redness, pain or swelling at the injection site; tissue damage or tissue death may occur after accidental injection outside a vein.

Other side effects:

Very common: may affect more than 1 in 10 people
- Hair loss (alopecia, in 60-90 % of treated cases. It involves poor beard growth in men. Hair loss is related to how much epirubicin treatment you are given; in most case hair normally regrows when your treatment course ends.
- Red coloration of urine for 1 to 2 days after administration.

Common: may affect up to 1 in 10 people
- Infection.
- Hot flashes.
- Mucous membrane inflammation (mucositis (can occur 5 to 10 days after the start of the treatment)), inflammation of the mucous membrane of the oesophagus (oesophagitis), inflammation of the mucous membrane of the mouth (stomatitis), vomiting, diarrhoea, dehydration, nausea (nausea and vomiting often occur within the first 24 hours (in nearly all patients), loss of appetite (anorexia).
- Bladder infection, inflammation of the bladder, sometimes bleeding, local reactions like burning sensations and frequent urge to urinate have been observed after administration into the bladder.
- Redness at infusion site.

Uncommon: may affect up to 1 in 100 people
- Redness along the veins (phlebitis), vascular inflammation with the forming of a blood

clot, often felt as a painful somewhat hard core with above it red skin (thrombophlebitis).

Rare: may affect up to 1 in 1,000 people
- Dizziness.
- Increased frequency of heart beat arising from lower chambers of the heart (ventricular tachycardia), slow heart rhythm (bradycardia), cessation of impulse transmission in the heart (AV block, bundle-branch block).
- Skin rash with formation of little bumps (urticaria) or with severe itching (pruritis), redness along the vein that was used for the injection.
- Increased blood level of uric acid (hyperuricaemia).
- Absence of menstruation, lack of sperm cells in sperm.
- Generally feeling unwell, weakness, fever, chills, changes in levels of certain enzymes (transaminase).

Not known: frequency cannot be estimated from the available data
- Certain disorder of the nerves (peripheral neuropathy), headache.
- Inflammation of the eye (conjunctivitis).
- Decrease of fraction of blood pumped out of a ventricle with each heart beat (asymptomatic drops in left ventricular ejection fraction).
- Thickening or hardening of the walls of the veins (phlebosclerosis).
- Local reactions, rash, itch, skin changes, redness, flushes, changes in skin and nail (hyperpigmentation), sensitivity to light (photosensitivity) or allergic reaction in the case of radiation (radiation-recall reaction).
- Increased amount of proteins in urine (proteinuria) in patients who were treated with a high dose.
- Swelling, pain, burning sensation, bleeding, ulcers or dark areas (pigmentation) in your mouth.

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

Store in a refrigerator (2-8 °C).
Store and transport refrigerated.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first opening this medicine should be used immediately.

After dilution (in 0.9 % (9 mg/ml) sodium chloride or 5 % (50 mg/ml) glucose solution) to a concentration of 0.1 mg/ml chemical and physical in-use stability has been demonstrated for 4 days at 25 °C and for 14 days at 2-8 °C.

After dilution (in 0.9 % (9 mg/ml) sodium chloride or 5 % (50 mg/ml) glucose solution) to a concentration of 1.0 mg/ml chemical and physical in-use stability has been demonstrated for 7 days at 25 °C and for 14 days (0.9 % (9 mg/ml) sodium chloride) or 7 days (5 % (50 mg/ml) glucose solution) at 2-8 °C.

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 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.

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to a mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15-25 °C).

Do not use this medicine if you see visual signs of deterioration.

6. Contents of the pack and other information

What Epirubicin contains

- The active substance is epirubicin hydrochloride; 1 ml contains 2 mg epirubicin hydrochloride.
- The other ingredients (excipients) are sodium chloride (see section 2 “Epirubicin contains sodium”), hydrochloric acid (for pH adjustment) and water for injections.

What Epirubicin looks like and contents of the pack

Epirubicin is a medicine in the form of a clear red solution for injection/infusion. It is delivered in glass injection vials with bromobutyl rubber stoppers and aluminium flip off seals with 25 ml (50 mg) or 100 ml (200 mg) of solution for injection/infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Generics UK Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
UK

Manufacturer

This medicinal product is authorised in the Member States of the EEA under the following names:
[To be completed nationally]

This leaflet was last revised in {10/2015}.

The following information is intended for medical and healthcare professional only:

PREPARATION GUIDE FOR USE WITH Epirubicin , SOLUTION FOR INJECTION OR INFUSION

It is important that you read the entire contents of this procedure prior to the preparation of either the Epirubicin solution for injection or infusion.

1. FORMULATION

Epirubicin hydrochloride 2 mg/ ml solution for injection/infusion.
Excipients:
sodium chloride
hydrochloric acid (for pH adjustment)
water for injections

2. PRESENTATION

Store in a refrigerator (2-8 °C).
Store and transport refrigerated.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first opening the medicinal product should be used immediately.

After dilution (in 0.9 % (9 mg/ml) sodium chloride or 5 % (50 mg/ml) glucose solution) to a concentration of 0.1 mg/ml chemical and physical in-use stability has been demonstrated for 4 days at 25 °C and for 14 days at 2-8 °C.

After dilution (in 0.9 % (9 mg/ml) sodium chloride or 5 % (50 mg/ml) glucose solution) to a concentration of 1.0 mg/ml chemical and physical in-use stability has been demonstrated for 7 days at 25 °C and for 14 days (0.9 % (9 mg/ml) sodium chloride) or 7 days (5 % (50 mg/ml) glucose solution) at 2-8 °C.

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 prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C.

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to a mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15-25 °C).

2.1 Epirubicin hydrochloride vial:

Epirubicin is delivered in amber coloured, 30 ml or 100 ml Type I moulded glass vials with fluorinated polymer coated bromobutyl rubber stopper and flip off aluminium seal, with resp. 25 ml and 100 ml solution for injection/infusion.

Each carton contains a single vial.

Not all pack sizes may be marketed

2.2 Solvent for epirubicin hydrochloride

Epirubicin can be diluted in NaCl 0.9 % (9 mg/ml) or glucose 5 % (50 mg/ml) and be administered intravenously. The solution must be prepared immediately prior to use.
For intravesical administration the product must be diluted with NaCl 0.9 % (9 mg/ml) or sterile water. The concentration of the dilution has to be 0.6-2.6 mg/ml.

3. RECOMMENDATIONS FOR THE SAFE HANDLING

If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.

Preparation of an infusion solution should be performed in a designated aseptic area.

People working with Epirubicin are required to wear protective gloves, safety goggles and a mask.

Epirubicin can be diluted in NaCl 0.9 % (9 mg/ml) or glucose 5 % (50 mg/ml) and be administered intravenously. The solution must be prepared immediately prior to use.

For intravesical administration the product must be diluted with NaCl 0.9 % (9 mg/ml) or sterile water. The concentration of the dilution has to be 0.6-2.6 mg/ml.

The red solution should be clear and transparent.

Epirubicin contains no preservatives and is therefore only suitable for single use. After use the unused remainder should be destroyed according to the regulations for cytostatic agents. See also “Disposal”.

Inactivation of spilled or leaked medicinal product can be obtained with a 1 % sodium hypochlorite solution or simply with a phosphate buffering agent (pH >8) until the solution is decolourised. All cleaning materials are disposed of as mentioned under “Disposal”.

Pregnant women must avoid contact with cytostatic agents.

Excreta and vomit should be cleaned up with care.

In case of contact with eyes, wash them thoroughly with plenty of water.
Contact an ophthalmologist immediately.
In case of skin contact, thoroughly was 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.

A damaged vial must be treated with the same precautions and must be considered as contaminated waste. Contaminated waste must be stored in appropriate specially marked waste containers. See under “Disposal”.

4. PREPARATION OF THE SOLUTION

Epirubicin is only intended for intravenous or intravesical use.

4.1 PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

Epirubicin can be diluted in NaCl 0.9 % (9 mg/ml) or glucose 5 % (50 mg/ml) and be administered intravenously. The solution must be prepared immediately prior to use.

The concentration of the dilution has to be 0.6-2.6 mg/ml.

It is advisable that the red solution, which should be clear and transparent, is injected via the catheter of a free running intravenous infusion of NaCl 0.9 % (9 mg/ml) or glucose 5 % (50 mg/ml) over a period of up to a duration of 30 minutes (depending on the dose and the volume of the infusion). The needle should be properly placed in the vein. This method reduces the risk of thrombosis and extravasation that could lead to severe cellulites and necrosis. In case of extravasation, administration should be stopped immediately. Injection in small veins and repeated injection in the same vein can lead to venous sclerosis.

For the treatment with a high dose epirubicin hydrochloride can be administered as an intravenous bolus over 3 - 5 minutes or as an infusion up to 30 minutes duration.

4.2 PREPARATION FOR THE INTRAVESICAL ADMINISTRATION

For intravesical administration Epirubicin must be diluted with NaCl 0.9 % (9 mg/ml) or sterile water. The concentration of the dilution has to be 0.6-2.6 mg/ml.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose epirubicin hydrochloride required	Volume of 2 mg/ml epirubicin hydrochloride injection	Volume of diluent sterile water for injection or 0.9 % (9 mg/ml) NaCl	Total volume of 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

5. DISPOSAL

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