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, 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
2. What you need to know before you use Epirubicin
3. How to use Epirubicin
4. Possible side effects
5. How to store Epirubicin
6. Contents of the pack and other information

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 hydrochloride is used to treat a variety of cancers, either alone or in combination with other medicines. The way in which it is used depends upon the type of cancer that is being treated. It is useful in treating the following conditions:

- Breast and gastric cancers
- Bladder cancers

Epirubicin is also used to 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 to epirubicin hydrochloride, to any of the other ingredients of this medicine (listed in section 6) or to similar medicines,
- if your blood cell count is too low as epirubicin can lower your blood count further. This is measured by health care personnel.
- if you have severe liver disease
- if you have been treated with high doses of some other anti-cancer medicines including doxorubicin and daunorubicin which belong to the same group of medicines as epirubicin (called anthracyclines). They have similar side effects (including those effects on the heart).
- if you have suffered or currently have problems with your heart
- if you have a severe infection

You must discontinue breast feeding before being given Epirubicin.

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Epirubicin

- to ensure the number of cells in your blood does not drop too low and you are not ill with a severe infection. Your doctor will regularly check this,
- if you are experiencing severe inflammation or ulcers in your mouth,
- to check the level of uric acid in your blood. Your doctor will regularly check this,
- if you have liver or kidney disease. Epirubicin may not be suitable for you or a reduced dose may have to be used.
- to ensure your heart is working properly. Your doctor will regularly check this by doing regular heart function tests.
- if you have received or are receiving radiotherapy to the chest area,
- if you are planning to start a family, whether you are male or female,
- if you are elderly.

During treatment

Extravasation (leakage of the solution out of the vein) of epirubicin may cause local pain, lesions and necrosis (death of living tissue) of surrounding tissue. If this occurs, the injection should be immediately stopped.

Other medicines and Epirubicin

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

Epirubicin should not be used:
- if you have been treated 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 their effects on the heart)
- 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, cyclophosphamine, 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).

- **quine** (a medicine used for treatment of malaria and for leg cramps); quine may speed up the distribution of epirubicin into the body, which may have a negative effect on the red blood cells.

- **dextrazoxane** (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 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**

If you become pregnant whilst receiving this medicine you should inform your doctor immediately. Both men and women should use effective contraception during treatment with Epirubicin and for 6 months after treatment with epirubicin has finished.

**Breast-feeding**

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

**Fertility**

Epirubicin can have an anti-fertility effect. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

**Driving and using machines**

You may feel and/or be sick after being given this medicine, therefore special care should be taken when driving or using machines.

**Epirubicin contains sodium.**

This medicinal product contains 3.6 mg sodium per ml. To be taken into consideration by patients on a
controlled sodium diet.

3. How to use Epirubicin

The dose of medicine given to you will depend on the type of cancer you have, your health, how well your liver and kidney are working and any other medicines you may be taking.

Method of administration, like the frequency of administration and duration of treatment, will depend on the route of administration as detailed below:

**By injection or infusion into a vein**
The medicine 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. You may be given another dose of this medicine in 3 weeks.

**By injection into the bladder through a tube (‘catheter’) (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 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.

When emptying your bladder after the medicine has been given, take care that your urine does not come into contact with your skin. In case contact does happen, thoroughly wash the affected area with soap and water but do not scrub.

While you are receiving this medicine your doctor will take regular blood tests. This is to measure the effect the drug is having. Your doctor will also do regular tests on how your heart is working.

If the medicine has been added to a bag of fluid for injection, or to be given into the bladder, it should be labelled with the strength of the medicine, volume and the time after which it should not be used.

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, however, tell your doctor or pharmacist if you have any concerns.

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 preleukaemic 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 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.

**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.
- Sudden feeling of feverish heat.
- 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).
- Headache
**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).
- Increased blood level of uric acid (hyperuricaemia).
- Absence of menstruation, lack of sperm cells in sperm.
- Generally feeling unwell, weakness, fever, chills and changes in levels of certain enzymes (transaminase).

**Not known**: frequency cannot be estimated from the available data
- 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, changes in skin and nail (hyperpigmentation), sensitivity to light (photosensitivity) or allergic reaction in the case of radiation (radiation-recall reaction).
- 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 the Yellow Card Scheme at: 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 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 vial label and outer carton 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 dispose of 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.
- The other ingredients are sodium chloride, water for injections and hydrochloric acid used as a pH adjuster.

**What Epirubicin looks like and contents of the pack**
Epirubicin is in the form of a solution for injection.

Each millilitre (ml) of solution contains 2 milligrams (mg) of epirubicin hydrochloride. The medicine is presented in glass containers called vials, containing 10 mg (5 ml), 20 mg (10 ml), 50 mg (25 ml) and 200 mg (100 ml) of epirubicin hydrochloride.
The vials are available in packs of 1, 5 or 10 vials of 5 ml, 10 ml, 25 ml or 100 ml. Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.

**Manufacturer(s)**

Haupt Pharma GmbH, Pfaffenrieder Strasse 5, 82 515 Wolfratshausen, Germany

or

Laboratoires Thissen S.A - Rue de la Papyrée 2-6 - B-1420 Braine-l'Alleud - Belgium

Or

MYLAN S.A.S., 117 allée des Parcs - 69800 SAINT-PRIEST, FRANCE.

This leaflet was last revised in July 2016

**Other sources of information**

Detailed information on this medicine is available on the website of the MHRA.
The following information is intended for healthcare professionals only:

For intravenous injection and intravesical administration

**Incompatibilities**

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug, which includes sodium bicarbonate containing solutions. Only the diluents detailed in ‘Dilution Instructions’ 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).

**Dilution Instructions**

The injection may be given via the tubing of a free-running intravenous saline infusion. Where the injection is to be administered after dilution, the following instructions should be followed.

Epirubicin (hydrochloride) 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 vials should be discarded immediately.

**Safe Handling**

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

**Storage**

Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

In use: Epirubicin (hydrochloride) 2 mg/ml injection may be further diluted as detailed above. The infusion solution is chemically stable when stored in infusion bags prepared under full aseptically controlled conditions for 60 minutes at 25°C. From a microbiological point of view however, 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°C unless dilution has taken place in controlled and validated aseptic conditions.