Package leaflet: Information for the user

Epirubicin hydrochloride 2 mg/ 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, 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

Epirubicin belongs to a group of active substances called anthracyclins. These cytotoxic active substances are used to treat cancer.

Epirubicin is used in the treatment of:
- breast cancer
- advanced ovarian cancer
- stomach cancer
- small cell lung cancer (special form of lung cancer)
- superficial or very localised cancer of the bladder.

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) or to anthracyclines [e.g. doxorubicin and daunorubicin]
- if you are allergic to anthracenediones (a group of medicines used to treat cancer)
- if you have a persistent inhibition of blood cell production in the bone marrow due to previous treatment with other cytotoxic medicinal products or radiotherapy
- if you have been treated with the maximum dose of epirubicin or other anthracyclines (e.g. doxorubicin and daunorubicin) and anthracenediones (medicines used to treat cancer)
- if you have suffered or currently have problems with your heart (e.g. heart rhythm disorders, reduced heart function, heart attack, heart muscle disorder, acute inflammation of the heart, unstable angina pectoris)
- if you suffer from a systemic infection
- if you have severe liver problems
- if you are breast feeding.

When administered intravesically (directly into the bladder), do not use epirubicin:
- if the cancer has penetrated the bladder wall

- if you have an infection of the urinary tract
- if there are problems inserting the catheter into the bladder
- if you have pain or inflammation in your bladder
- if you have blood in your urine
- if there is a large volume of urine left in your bladder after you attempt to empty it
- if you have a contracted bladder.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Epirubicin.

- if your numbers of white and red blood cells and platelets are reduced .
- if you suffer from stomatitis or mucositis (sore lips or ulcers in your mouth).
- if your liver and kidneys are not working properly
- if you have received or are receiving radiotherapy to the chest area or are receiving medications that might have side effects on your heart.
- if you notice a sensation of discomfort close to or at the injection site during the infusion (possible leakage in the surrounding tissue).
- if you have recently received or want to receive any vaccination.
- if you have previously received trastuzumab (a medicine used to treat cancer).

Children
The safety and efficacy of Epirubicin in children has not been established.

Other medicines and epirubicin:
Tell your doctor or pharmacist if you have recently taken any other medicines:
- cimetidine (a medicine usually used to treat stomach ulcers and heartburn). Cimetidine can make the effects of epirubicin stronger
- other medicines that may affect your heart, for example other medicines against cancer (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), calcium channel blockers (e.g. dexverapamil used to control high blood pressure, chest pain, and irregular heart beat), or concomitant (or prior) radiotherapy to the mediastinal area
- quinine (a medicine used for treatment of malaria and for leg cramps)
- other medicines that may affect the blood cell count, e.g. cytostatic medicine, sulphonamide, chloramphenicol (used to treat infection), diphenylhydantoin (used to treat epilepsy), aminopyrine-derivate (used to relieve pain), antiretroviral agents (used to treat HIV-infection)
- other medicines that may affect your liverpaclitaxel (medicine used for cancer): treatment of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the 2 medicines.
- docetaxel (medicine used for cancer)
- interferon alpha-2b (a medicine used in some cancers and lymphomas and for some forms of hepatitis)
- dexrazoxane (used to prevent chronic cumulative cardiotoxicity caused by epirubicin)
- trastuzumab (treatment for cancer); epirubicin should not be taken within 27 weeks after taking trastuzumab.

If you need to have any vaccinations, you must inform your doctor that you are being treated with epirubicin before receiving the vaccination.

Pregnancy, breast-feeding and fertility

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. Epirubicin hydrochloride may cause birth 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. If pregnancy occurs during treatment with epirubicin, genetic counseling is recommended.

Breast-feeding
You should stop breast feeding before starting treatment with this medicine as some of the meidine may get into your milk and possibly harm your child.

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

Epirubicin may cause lack of menstrual cycles or premature menopause in premenopausal women.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed with epirubicin. However, epirubicin may cause nausea and vomiting, which can temporarily affect your ability to drive and use machines.

Important information about some of the ingredients of Epirubicin hydrochloride 2 mg/ml solution for injection or infusion

Each 10 mg/ 5 ml vial contains 17.7 mg sodium (main component of cooking/table salt). This is equivalent to 0.88 % of the recommended maximum daily dietary intake of sodium for an adult.

Each 50 mg/ 25 ml vial contains 88.5 mg sodium (main component of cooking/table salt). This is equivalent to 4.4 % of the recommended maximum daily dietary intake of sodium for an adult.

Each 100 mg/ 50 ml vial contains 177 mg sodium (main component of cooking/table salt). This is equivalent to 8.85 % of the recommended maximum daily dietary intake of sodium for an adult.

Each 200 mg/ 100 ml vial contains 354.1 mg sodium (main component of cooking/table salt). This is equivalent to 17.7 % of the recommended maximum daily dietary intake of sodium for an adult.

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.

The 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.

The recommended dosage of Epirubicin hydrochloride is 60 mg/m^2 to 90 mg/m^2 body surface area. It is given as an intravenous injection, i.e. into a blood vessel, over three to five minutes. The injection is given every three weeks.

In the treatment of small cell lung cancer, a higher dose of 120 mg/m^2 of body surface area is given by injection into a vein over three to five minutes or as an infusion (drip) of up to 30 minutes, every three weeks.

For the treatment of breast cancer your doctor will decide on the dosage and regimen.

The dosage will be reduced if you have a low level of white blood cells and platelets in your body, if you have liver or renal problems, or if the medicinal product is used in combination with other anticancer medicinal product.

Epirubicin can also be given directly into the bladder to treat superficial bladder cancer or to stop recurrence after bladder surgery to remove the cancer. The dose will depend upon the type of bladder cancer.

To avoid undue dilution of epirubicin with urine you are advised not to drink 12 hours before the treatment.

Your general condition will be closely observed before, during and after the treatment with epirubicin.

If you are given more Epirubicin than you should
In case you were given a higher dosage of epirubicin than required especially your heart function and count of blood cells will be closely monitored. The occurring side effects may be more severe. If you have any further questions on the use of this medicine , ask your doctor or pharmacist or nurse.

4. Possible side effects

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

Please tell your doctor immediately if you notice any side effects and discuss any further actions with him.

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

Epirubicin may cause a red colouration of the urine for one or two days after administration. This is normal and nothing to worry about.

Very common: may affect more than 1 in 10 people
- infection
- inhibition of blood cell production in the bone marrow (myelosuppression)

- decreased number of white blood cells (leukopenia)
- decreased number of a special form of white blood cells (granulocytopenia and neutropenia)
- low level of certain white blood cells accompanied by fever (febrile neutropenia)
- decrease in red blood cells (anaemia)
- decreased number of platelets (thrombocytopenia)
- loss/lack of appetite
- inflammation of a mucous membrane (mucositis), inflammation inside the mouth (stomatitis), being sick (vomiting), watery stools or bowel movements (diarrhoea), feeling sick (nausea), which can result in loss of appetite and abdominal pain
- hair loss (alopecia) normally reversible
- your urine may have a red colour for one to two days after treatment.

Common: may affect up to 1 in 10 people
- impaired heart function (congestive heart failure) which may lead to shortness of breath (dyspnoea), accumulation of fluid in the legs (oedema), enlargement of the liver, accumulation of fluid in the abdominal cavity (ascites), accumulation of fluid in the lung (pulmonary oedema), accumulation of fluid between thorax and lung (pleural effusions) or third heart sound (gallop rhythm)
- feeling very dry and thirsty (dehydration)
- hot flashes
- inflammation of the oesophagus, burning sensation of the mucosa of the mouth with areas of painful erosions
- local skin toxicity, rash, itching
- absence of menstruation
- redness along the infusion vein (infusion site erythema), severe damage of the tissue following leakage of the injection into the surrounding tissue Feeling of discomfort (malaise), feeling of weakness (asthenia), fever
- changes in the level of certain liver enzymes (so-called transaminases)
- changes in heart function without any symptoms (asymptomatic drops in left ventricular ejection fraction)
- bladder inflammation with pain when passing urine (chemical cystitis), sometimes with blood in the urine (haemorrhagic) following administration into the bladder

Uncommon: may affect up to 1 in 100 people
- certain types of blood cancer (acute lymphocytic leukaemia, acute myelogenous leukaemia)
- pinkeye (conjunctivitis), inflammation of the cornea of the eye (keratitis)
- gastric erosions and lesions, gastrointestinal bleeding, increased colouring of the mucosa of the mouth
- vein inflammation (phlebitis), vein inflammation related to a blood clot (thrombophlebitis)
- skin changes, skin reddening (erythema), flushes, increased pigmentation of skin and nails, increased sensitivity to light (photosensitivity), increased sensitivity to irradiated skin (radiation-recall reaction)

Rare: may affect up to 1 in 1,000 people
- severe allergic reaction (anaphylaxis) including allergy-like reaction (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus (itching), fever and chills; allergic reactions after administration of the medicine into the bladder
- toxic effects on the heart like abnormalities in ECG, different forms of irregular heart beat (arrhythmias) or heart muscle disease (cardiomyopathy), life-threatening irregular heart beat (ventricular tachycardia), slow heart rate, defect of the heart's electrical conduction system (AV block, bundle-branch block)

- hives
- chills
- dizziness
- lack of sperm in the semen (azoospermia)
- increased levels of uric acid in the blood

Very rare: may affect up to 1 in 10,000 people
- shock

Not known (frequency cannot be estimated from the available data):
- infection of the lungs (pneumonia), systemic infection (sepsis), septic shock
- bleeding and inadequate oxygen supply of tissue may occur as a result of inhibition of blood cell production in the bone marrow (myelosuppression)
- occlusion of blood vessel by dislodged blood clot (thromboembolism) including occlusion of blood vessel by dislodged blood clot in the lungs (pulmonary emboli)
- thickening of the vein walls, local pain, severe cellulitis

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.

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 national reporting system.

For United Kingdom
You can report side effects directly via the Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

For Ireland
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 to 8 °C). Do not freeze. Keep 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 carton and vial label after EXP. The expiry date refers to the last day of that month. The pharmacist will check this when your medicine is prepared for you. If the solution is cloudy after preparation, the pharmacist will dispose of it safely.

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 hydrochloride 2 mg/ml solution for injection contains

The active substance is epirubicin hydrochloride. Each ml of solution for injection or infusion contains 2 mg of epirubicin hydrochloride.

The other ingredients are hydrochloric acid, sodium chloride and water for injections.

What Epirubicin hydrochloride 2 mg/ml solution for injection or infusion looks like and contents of the pack

Epirubicin contains 10 mg, 50 mg, 100 mg and 200 mg of the active ingredient, epirubicin hydrochloride in single glass vials.

Pack sizes:-
1 x 5 ml vial
1 x 25 ml vial
1 x 50 ml vial
1 x 100 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

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

Belgium	Epirubicinehydrochloride Fresenius Kabi 2 mg/ml oplossing voor injectie of infusie
Bulgaria	Епирубицин Каби 2 mg/ml инфузионен разтвор
Denmark	Epirubicin ”Fresenius Kabi”
Estonia	Epirubicin Kabi 2 mg/ml
Hungary	Epirubicin Kabi 2 mg/ml oldatos injekció vagy infúzió
Ireland	Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion
Lithunian	Epirubicin Kabi 2 mg/ml injekcinis/ infuzinis tirpalas

Malta	Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion
Netherlands	Epirubicinehydrochloride Fresenius Kabi 2 mg/ml oplossing voor injectie of infusie
Poland	Epirubicin Kabi
Portugal	Epirrubicina Kabi
Spain	Epirubicina Kabi 2 mg/ml solución inyectable o para perfusión
UK	Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion

This leaflet was last revised in July 2018

The following information is intended for healthcare professionals only:

A GUIDE FOR HOSPITAL STAFF

Epirubicin hydrochloride 2 mg/ ml solution for injection or infusion

(Epirubicin hydrochloride)

IMPORTANT: Refer to Summary of Product Characteristics before prescribing.

***Intravenous administration*.** Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose). 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 (see Warning and Precautions).

Discard any unused solution.

Intravesical administration. Epirubicin should be instilled using a catheter and retained intravesically for 1-2 hour. 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 urine at the end of the instillation.

Protective measures: 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 medicine.
- 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. 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.
- 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. In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Disposal

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