Patient leaflet: Information for the user

Epirubicin Hydrochloride 10 mg powder for solution for injection

Epirubicin Hydrochloride 50 mg powder for solution for injection

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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.

The name of your medicine is Epirubicin Hydrochloride 10 mg or 50 mg powder for solution for injection, which will be referred as Epirubicin hydrochloride throughout the leaflet.

What is in this leaflet

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

- Epirubicin hydrochloride contains the active substance epirubicin hydrochloride. It belongs to a group of medicines called cytotoxics used for chemotherapy. Epirubicin hydrochloride causes cells that are actively growing, such as cancer cells, to slow or stop their growth and increases the likelihood that they die. This medicine helps to selectively kill the cancer tissue rather than normal, healthy tissue.
- Epirubicin hydrochloride is used to treat a variety of cancers, either alone or in combination with other drugs. The way in which it is used depends upon the type of cancer that is being treated.
- It has been found to be particularly useful in the treatment of cancers of the breast, ovaries, stomach, bowel and lung. In addition, this medicine can be given to treat cancers of the blood forming tissues such as malignant lymphomas, leukaemias and multiple myeloma.
- Epirubicin hydrochloride can also be put directly into the bladder through a tube. This is sometimes used to treat abnormal cells or cancers of the bladder wall. It can also be used after other treatments to try and prevent such cells from growing again.

You must talk to a doctor if you do not feel better or if you feel worse.

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

Do not use Epirubicin hydrochloride:
- if you are allergic to epirubicin or any of the other ingredients of this medicine (listed in section 6) or similar chemotherapy drugs (anthracyclines or anthracenediones)
- if you have infections affecting multiple organs
- if you have a urine infection
- if you have inflammation of the bladder
- if you have invasive tumours penetrating the bladder
- if you have catheterisation problems (your doctor has problems inserting a catheter (tube) into your bladder)
- if you have presence of blood in your urine
- if you have decreased ability to produce blood cells leading to low blood cell counts, as it can lower them further
- if you have previously been treated with Epirubicin hydrochloride or similar chemotherapy drugs, as previous treatment with these medicines can increase the risk of side effects
- if you have suffered from a recent heart attack, poor functioning of the heart muscle, severe irregular heartbeat pattern, sudden pain in the chest, non-inflammatory disease of the heart muscle or any other severe heart trouble in the past, or are presently receiving treatment for this
- if you have severe liver disease
- if you are pregnant or breast-feeding

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Epirubicin hydrochloride:
- if your liver or kidneys are not working properly
- if you have had or are due to have any vaccination
- if you are currently suffering from acute toxicities such as
  - acute inflammation of the mouth
  - low white blood cell count
  - low platelet count or
  - infections in general
- if you are currently taking or have recently taken trastuzumab (a medicine used in the treatment of certain cancers). Trastuzumab can remain in the body for up to 7 months after you have stopped taking trastuzumab. If Epirubicin hydrochloride is used before this time, then your heart function should be carefully monitored
- in pregnant women, there have been a few reports that Epirubicin hydrochloride has been associated with heart problems in newborns and unborn babies, including foetal death.

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

Other medicines and Epirubicin hydrochloride
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, even those obtained without a prescription, particularly the following:

- ***Cimetidine*** (a drug usually used to treat stomach ulcers and heartburn). Cimetidine can make the effects of Epirubicin hydrochloride 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
- ***Trastuzumab*** therapy for treatment of cancer. Your doctor should avoid using Epirubicin

hydrochloride for up to 7 months after stopping trastuzumab when possible. If Epirubicin hydrochloride is used before this time, careful monitoring of cardiac function is recommended
- ***Vaccination*** with a live vaccine should be avoided in patients receiving Epirubicin hydrochloride
- ***Paclitaxel or Docetaxel*** (drugs used to treat cancer). When paclitaxel is given prior to Epirubicin hydrochloride, it may increase the concentration of Epirubicin hydrochloride in the blood. However when Paclitaxel and Docetaxel are given together and given after Epirubicin hydrochloride, they did not affect the concentration of Epirubicin hydrochloride
- ***Dexverapamil*** (used to treat some heart conditions)
- *interferon α2b* (a product used in some cancers and lymphomas and some forms of hepatitis).
- ***Dexrazoxane*** (used to prevent chronic cumulative cardiotoxicity caused by Epirubicin hydrochloride)
- ***Interferon α2b*** (used to treat cancers)

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. Avoid becoming pregnant while you or your partner is being treated with this medicine.
Both men and women should seek advice on fertility preservation before treatment.
If you are sexually active, you are advised to use effective birth control to prevent pregnancy.
Women of childbearing potential should be advised to use effective contraception during treatment with Epirubicin hydrochloride and for at least 6.5 months after the last dose. Males should use effective contraception during treatment and for at least 3.5 months after the last dose. It may cause birth defects, so it is important to tell your doctor if you think you are pregnant.

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. Do not breast-feed whilst receiving treatment with Epirubicin hydrochloride for at least 7 days after the last dose.

Fertility
Both men and women should seek advice on fertility preservation before treatment.
Men: There is a risk of sterility due to therapy with Epirubicin hydrochloride and male patients should consider storage of sperm before treatment. Men should use effective contraception during treatment and for at least 3.5 months after the last dose.
Women: Epirubicin hydrochloride may cause lack of menstrual cycles or premature menopause in premenopausal women. Women of childbearing potential should be advised to use effective contraception during treatment with Epirubicin hydrochloride and for at least 6.5 months after the last dose.

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.

Epirubicin hydrochloride may be prepared with a solution that contains sodium
This medicinal product may be prepared with a solution that contains sodium. Tell your doctor if you are on a low salt (sodium) diet.

Epirubicin hydrochloride contains methyl hydroxybenzoate
This medicine contains methyl hydroxybenzoate, which may cause allergic reactions (which may occur after treatment), and in rare cases, respiratory difficulties.

3. How to use Epirubicin hydrochloride

If you are prescribed Epirubicin hydrochloride it will be given to you by doctors or nurses experienced in giving chemotherapy.
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 upon 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 hydrochloride 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.

Regular checks by your doctor during Epirubicin hydrochloride treatment
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 hydrochloride 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 hydrochloride 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.

If you receive high doses of Epirubicin hydrochloride
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 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 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.

Very common (may affect more than 1 in 10 people)
- Infections
- Eye inflammation with red eyes and watery eyes
- A low red blood cell count (anaemia) that can leave you feeling tired and lethargic
- White blood cell counts (which fight infection) can drop, which increases the chance of infections and fever (leukopenia)
- Decreased thrombocytes (platelets in the blood that help the blood to clot) may occur, which could make you bruise or bleed when injured more easily
- Reduction in the number of certain types of white blood cells – granulocytes and neutrophiles (granulocytopenia and neutropenia)
- A reduction in certain types of white blood cells accompanied by fever (febrile neutropenia)
- Inflammation of the transparent part of the eye called cornea
- Hot flushes
- Inflammation of a vein
- Nausea
- Vomiting

- Inflammation of the mucous lining in the mouth
- Diarrhoea
- Hair loss
- Skin lesion
- Red coloured urine for 1 to 2 days after administration of Epirubicin hydrochloride
- Absence of menstruation
- Painful inflammation and ulceration of the mucous membranes lining the digestive tract
- Feeling generally unwell
- Fever
- Changes in levels of some liver enzymes
- After direct administration of Epirubicin hydrochloride into the bladder, inflammation (cystitis) is possible

Common (may affect up to 1 in 10 people)
- Reduced appetite/loss of appetite
- Lose water or body fluids
- Severe cardiac rhythm disorder (ventricular arrhythmia)
- Cardiac impulse conduction disorders
- Certain forms of heart rhythm disorders (AV block, bundle branch block)
- Slow heartbeat (bradycardia)
- Insufficient pumping of blood by the heart which can cause shortness of breath, accumulation of fluid, and abnormal heart rhythm
- Bleeding
- Redness of the skin
- Pain behind the breastbone, indigestion, and difficulty in swallowing due to inflammation in the oesophagus
- Pain or burning in the gastrointestinal tract
- Inflammation of the mucous membrane of the gastrointestinal tract
- Ulcers in the gastrointestinal tract
- Rash, itching
- Abnormal discolouration of nails
- Frequent urination
- Redness at the infusion site
- Chills
- Local reactions such as burning sensation
- Reduced heart function

Uncommon (may affect up to 1 in 100 people)
- High fevers, chills, general malaise, possible cold arms or legs due to blood poisoning
- Lung infection (pneumonia)
- Certain types of cancer of the blood (acute lymphatic leukaemia, acute myeloid leukaemia)
- Blockage in a blood vessel
- Swelling or pain in the legs or arms
- Blood clots in the lungs which causes chest pain and breathlessness
- Gastrointestinal tract bleeding
- Hives
- Skin redness
- Feeling of weakness

Please contact your doctor or nurse immediately if you notice any of the following side effects. Although they are rare these symptoms can be serious:

Rare (may affect up to 1 in 1,000 people)

- Sudden life-threatening allergic reaction. Symptoms include sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing
- Increased level of uric acid in the blood
- Heart damage (cardiotoxicity)
- Absence of sperm cells in the sperm
- Light headedness

Not known (frequency cannot be estimated from the available data)
- Life-threatening condition that occurs when the blood pressure is too low due to blood poisoning (septic shock)
- Life-threatening condition where the blood pressure is too low
- Insufficient oxygen supply to the tissue due to inhibited blood cell production in the bone marrow
- Appearance of dark spots inside the mouth
- Abdominal discomfort
- Skin redness or other reactions similar to scalding when exposed to sunlight or ultraviolet rays
- Changes in the skin where you previously received radiation treatment

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 or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Epirubicin hydrochloride

Keep this medicine out of the sight and reach of children.

Do not use Epirubicin hydrochloride after the expiry date which is stated on the vial label & carton after "EXP". The expiry date refers to the last day of that month.

If the solution is cloudy after preparation, the doctor or nurse who is preparing the medicine for you will dispose of it safely.

The unopened vials should be stored below 30°C in the original container until ready for use.

Reconstituted solution should be used immediately.

Do not throw away any medicines via wastewater or household water. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Epirubicin hydrochloride contains
- The active substance is epirubicin hydrochloride. Each vial contains 10mg and 50mg of epirubicin hydrochloride. After reconstitution, each vial contains 2mg/ml Epirubicin hydrochloride.
- The other ingredients are lactose monohydrate, methyl hydroxybenzoate, hydrochloric acid (for pH adjustment) and water for injections.

What Epirubicin hydrochloride looks like and contents of the pack
Epirubicin hydrochloride is a sterile freeze-dried orange red coloured lyophilised cake.

Epirubicin hydrochloride 10mg is produced in 10ml Type I moulded flint glass vial with 20mm rubber stoppers and 20mm aluminium flip-off tear-off seal.

Epirubicin hydrochloride 50 mg is produced in 50 ml Type I moulded flint glass vial with 20 mm rubber stoppers and 20 mm aluminium flip-off tear-off seal.

Each pack contains a single vial.

Marketing Authorisation Holder
Dawa Ltd, 5 Sandridge Close, Harrow, Middlesex, HA1 1XD, United Kingdom.

Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Limited,
9th floor, C.P. House, 97 – 107 Uxbridge Road, Ealing, London, W5 5TL.

Distributed By:
APC Pharmaceuticals & Chemicals (Europe) Limited,
9th floor, C.P. House,
97 – 107 Uxbridge Road,
Ealing, London W5 5TL

This leaflet was last revised in – 06/2024
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:
APC Pharmaceuticals & Chemicals (Europe) Ltd.,
9th floor, C.P. House,
97 – 107 Uxbridge Road,
Ealing, London W5 5TL
Telephone number: 0208 326 3220

A guide for hospital staff

IMPORTANT: Refer to Summary of Product Characteristics before prescribing.

Presentation:

Sterile, freeze-dried orange red coloured lyophilised cake containing 10mg and 50mg of epirubicin hydrochloride as a 2mg/ml solution in 0.9% sodium chloride solution.

Instructions for use, handling and disposal
Preparation of the freeze-dried powder for intravenous use.

The product should be dissolved in 5 ml or 25 ml 0.9% sodium chloride or water for injections to get the final concentration of 2 mg/ml. The vial contents will be under a negative pressure. To minimise aerosol formation during reconstitution, particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided. After gentle agitation the reconstituted solution will be transparent and red in appearance.

Uses:
Epirubicin hydrochloride has produced responses in a wide range of neoplastic conditions including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma.
Intravesical administration of Epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and the prophylaxis of recurrences after transurethral resection.

Dosage and administration:
Intravenous administration:
Epirubicin hydrochloride is not active when given orally and should not be injected intramuscularly or intrathecally.
Epirubicin hydrochloride solution should be administered only under the supervision of a qualified physician experienced in antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin hydrochloride in particular requires the availability of facilities for the care of possible clinical complications due to profound myelosuppression.
It is advisable to give the drug via 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 hydrochloride 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.

Conventional doses:
When Epirubicin hydrochloride is used as a single agent, the recommended dosage in adults is 60-90mg/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.
Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopaenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in cases of liver impairment.

High doses:
Epirubicin hydrochloride as a single agent for the treatment of lung cancer at high doses should be administered according to the following regimens:
• small cell lung cancer (previously untreated): 120mg/m^2 day 1, every 3 weeks
• non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135mg/m^2 day 1 or 45mg/m^2 days 1, 2, 3, every 3 weeks
• breast cancer: in the adjuvant treatment of early breast cancer patients with positive lymph nodes,

intravenous doses of Epirubicin hydrochloride ranging from 100mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.
The drug should be given as an I.V. bolus over 3-5 minutes or as an infusion up to 30 minutes. Lower doses (60-75mg/m^2 for conventional treatment and 105-120mg/m^2 for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dosage per cycle may be divided over 2-3 successive days.
When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin hydrochloride is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase in overall toxicity. Moderate liver impairment (bilirubin: 1.4-3mg/100ml) requires a 50% reduction of dose, while severe impairment (bilirubin >3 mg/100ml) necessitates a dose reduction of 75%.
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin hydrochloride excreted by this route.

Intravesical administration:
Epirubicin hydrochloride may be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be used in this way for the treatment of invasive tumours which have penetrated the bladder wall where systemic therapy or surgery is more appropriate.
Epirubicin hydrochloride has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial bladder tumours in order to prevent recurrences.
While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30mg/50ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80mg/50ml. For prophylaxis, 4 x weekly administrations of 50mg/50ml followed by 11 x monthly instillations at the same dosage, is the schedule most commonly used.
The solution should be retained intravesically for 1 hour. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During instillation, the patient should be rotated occasionally and should be instructed to void at the end of the instillation time.

Contraindications
Hypersensitivity to epirubicin or any other component of the product, other anthracyclines or anthracenediones.
• Lactation

Intravenous use:
• persistent myelosuppression
• severe hepatic impairment
• severe myocardial insufficiency
• recent myocardial infarction
• severe arrhythmias
• previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see section 4.4)
• patients with acute systemic infections
• unstable angina pectoris
• myocardiopathy

Intravesical use:
• urinary tract infections
• inflammation of the bladder
• haematuria
• invasive tumours penetrating the bladder
• catheterisation problems

Warnings & Precautions

(refer to the SPC, section 4.4 – special warnings & precautions for use, for further information)

General
Epirubicin hydrochloride should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections) of prior cytotoxic treatment before beginning treatment with Epirubicin hydrochloride.
While treatment with high doses of Epirubicin hydrochloride (e.g., ≥ 90mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90mg/m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucosal inflammation may be increased. Treatment with high doses of Epirubicin hydrochloride does require special attention for possible clinical complications due to profound myelosuppression.

Cardiac function – Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.
The risk of developing CHF increases rapidly with increasing total cumulative doses of Epirubicin hydrochloride in excess of 900mg/m^2; this cumulative dose should only be exceeded with extreme caution (see section 5.1 - pharmacodynamic properties, clinical studies).
Cardiac function should be assessed before patients undergo treatment with Epirubicin hydrochloride and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment.
Given the risk of cardiomyopathy, a cumulative dose of 900mg/m^2 Epirubicin hydrochloride should be exceeded only with extreme caution.
Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with anthracyclines such as Epirubicin hydrochloride. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as Epirubicin hydrochloride should not be used currently in combination except in a well controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.
The reported half-life of trastuzumab is variable. The substance may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.
If symptomatic cardiac failure develops during trastuzumab therapy after Epirubicin hydrochloride therapy, it should be treated with the standard medications for this purpose.
There have been sporadic reports of foetal/ neonatal cardiotoxic events including foetal death following in utero exposure to Epirubicin hydrochloride (see section **4.6**).
(Please refer to the SPC, section **4.4** - special warnings & precautions for use, for further information)
Haematologic toxicity - As with other cytotoxic agents, Epirubicin hydrochloride may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with Epirubicin hydrochloride, including differential white blood cell (WBC) counts.
Secondary leukaemia - Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including Epirubicin hydrochloride.
Gastrointestinal - Epirubicin hydrochloride is emetogenic. Mucosal inflammation/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations.
Liver function - The major route of elimination of Epirubicin hydrochloride is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with Epirubicin hydrochloride. Lower doses of Epirubicin hydrochloride are recommended in patients with elevated bilirubin or AST levels.
Renal function - Serum creatinine should be assessed before and during therapy.
Dosage adjustment is necessary in patients with serum creatinine >5mg/dL.
Effects at site of injection - Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (see section **4.2**).
Extravasation - Extravasation of Epirubicin hydrochloride during intravenous injection may produce local

pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (please refer to relevant labels for use). The patient's pain may be relieved by cooling down the area and keeping it cool, using hyaluronic acid and DMSO. If extravasation occurs the patient should be monitored closely during the subsequent period of time, as tissue necrosis at the extravasation site may occur after several weeks from the extravasation episode.
Other - As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of Epirubicin hydrochloride.
Tumour-lysis syndrome - Epirubicin hydrochloride may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumour-lysis syndrome).
Immunosuppressant effects/increased susceptibility to infections - Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including Epirubicin hydrochloride, may result in serious or fatal infections (see section **4.5**). Vaccination with a live vaccine should be avoided in patients receiving Epirubicin hydrochloride. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.
Reproductive system - Epirubicin hydrochloride can cause genotoxicity. Men and women treated with Epirubicin hydrochloride should adopt appropriate contraceptives during and for a period after treatment with Epirubicin hydrochloride (see section **4.6**).
Intravesical administration of Epirubicin hydrochloride may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction.
Intra-arterial administration of Epirubicin hydrochloride (transcatheter arterial embolisation for the localised or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of Epirubicin hydrochloride) localised or regional events which include gastroduodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Excipient with known effect
This medicinal product may be further prepared for administration with sodium containing solutions (see section **4.2** and **6.6**) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.
For additional warnings and precautions for other routes of administration refer to the SPC section 4.4 – special warnings & precautions for use*.*

Interactions:
Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects (see section **4.4**).
The use of Epirubicin hydrochloride in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.
Epirubicin hydrochloride is extensively metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect Epirubicin hydrochloride metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section **4.4**).
Anthracyclines including Epirubicin hydrochloride should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored.
Vaccination with a live vaccine should be avoided in patients receiving Epirubicin hydrochloride. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.
Cimetidine increased the AUC of Epirubicin hydrochloride by 50% and should be discontinued during treatment with Epirubicin hydrochloride.
When given prior to Epirubicin hydrochloride, paclitaxel can cause increased plasma concentrations of unchanged Epirubicin hydrochloride and its metabolites, the latter being, however, neither toxic nor active.
Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.
Refer to the SPC, section 4.5 – interaction with other medicinal products and other forms of

interaction, for further information.

Adverse reactions
The following undesirable effects have been observed and reported during treatment with Epirubicin hydrochloride with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (<1/10,000), not known (frequency cannot be estimated form the available data)

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Very common	Infection, conjunctivitis
	Uncommon	Sepsis*, pneumonia*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Uncommon	Acute lymphocytic leukaemia, acute myeloid leukaemia
Blood and lymphatic system disorders	Very common	Leukopenia, neutropenia, anaemia, febrile neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction*
Metabolism and nutrition disorders	Common	Decreased appetite, dehydration*
	Rare	Hyperuricemia*
Eye disorders	Very common	Keratitis
Cardiac disorders	Common	Ventricular tachycardia, atrioventricular block, bundle-branch block, bradycardia, cardiac failure congestive
Vascular disorders	Very common	Hot flush, phlebitis*
	Common	Haemorrhage*, flushing*
	Uncommon	Embolism, embolism arterial*, thrombophlebitis*
	Not known	Shock*
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary embolism*
Gastrointestinal disorders	Very common	Mucosal inflammation, stomatitis, vomiting, diarrhoea, nausea
	Common	Gastrointestinal pain*, gastrointestinal erosion*, gastrointestinal ulcer*
	Uncommon	Gastrointestinal haemorrhage*
	Not known	Abdominal discomfort, pigmentation buccal*
Skin and subcutaneous tissue disorders	Very common	Alopecia, skin toxicity
	Common	Rash/pruritus, nail pigmentation*, skin disorder, skin hyperpigmentation*
	Uncommon	Urticaria*, erythema*
	Not known	Photosensitivity reaction*
Renal and urinary disorders	Very common	Chromaturia*†
Reproductive system and breast disorders	Very common	Amenorrhoea

General disorders and administration site conditions	Very common	Malaise, pyrexia*
	Common	Chills*
	Uncommon	Asthenia
Investigations	Very common	Transaminases abnormal
	Common	Ejection fraction decreased
Injury, poisoning and procedural complications	Very common	Chemical cystitis*§
	Not known	Recall phenomenon*Δ

* ADR identified post-marketing.
† Red colouration of urine for 1 to 2 days after administration.
§ Following intravesical administration.
Δ Hypersensitivity to irradiated skin (radiation recall reaction).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Pregnancy
There are limited amount of data from the use of Epirubicin hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section **5.3**).
Experimental data in animals suggest that Epirubicin hydrochloride may cause foetal harm when administered to a pregnant woman. Avoid the use of Epirubicin hydrochloride during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of Epirubicin hydrochloride during the 2nd and 3rd trimesters.
If Epirubicin hydrochloride is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. There have been sporadic reports of foetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of foetal death from suspected anthracycline-induced cardiotoxicity following in utero exposure to Epirubicin hydrochloride in 2nd and/or 3rd trimesters (see section **4.4**). Monitor the foetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.
Epirubicin hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
It is not known whether Epirubicin hydrochloride is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Epirubicin hydrochloride, lactating women should be advised not to breastfeed during treatment with Epirubicin hydrochloride and for at least 7 days after the last dose.

Impairment of fertility
Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Men undergoing treatment with Epirubicin hydrochloride are advised not to father a child during treatment and to seek advice regarding cryopreservation of sperm prior to treatment due to the possibility of irreversible infertility caused by therapy, and/or to use individual genetic counselling for male or female patients intending to have a child after treatment with Epirubicin hydrochloride.

Males

The recommended duration of conception in male patients should be until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days. The same would be true for a pure aneugenic compound.

Females

It takes approximately 6 months for an oocyte to mature from the primordial to the Graafian stage. Animal studies have demonstrated that oocytes exposed to a genotoxic compound at the earliest stage of maturation led to an increase in foetal malformation in pregnancies, whilst exposure of oocytes at the

pre-ovulatory stage entailed the highest abortion rate.

Refer to SPC section 4.6 - pregnancy and lactation, for further information.

Effects on ability to drive and use machines

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

Overdosage:

Acute overdosage with Epirubicin hydrochloride will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucosal inflammation) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section **4.4**). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment:

Symptomatic Epirubicin hydrochloride cannot be removed by dialysis.

Pharmaceutical precautions:

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 hydrochloride should wear protective clothing: goggles, gowns and disposable gloves and masks.

• 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. 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.

Discard any unused solution.

Incompatibilities

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

Epirubicin hydrochloride should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Epirubicin hydrochloride can be used in combination with other antitumour agents, but it is not recommended that it be mixed with other drugs.

Shelf life

Shelf life of the product as packaged for sale: 2 years

Storage

Store unopened vials below 30°C in the original container until ready for use.

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

Shelf life after first opening the container

From a microbiological point of view 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 – 8 °C, unless reconstitution has taken place in controlled and validated conditions.

PL 30684/0141 + PL 30684/0142

This leaflet was prepared in 06/2024.