Patient leaflet: Information for the user

Pharmorubicin® 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, please 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.

What is in this leaflet:

1. What Pharmorubicin is and what it is used for

- Pharmorubicin is an injection that contains epirubicin hydrochloride. It belongs to a group of medicines called cytotoxics used for chemotherapy. Pharmorubicin 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.

- Pharmorubicin 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.

- Pharmorubicin 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 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 Pharmorubicin

Do not use Pharmorubicin:

- 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 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 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 Pharmorubicin or similar chemotherapy drugs, as previous treatment with these medicines can increase the risk of side effects
- if you have suffered from 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 Pharmorubicin:
- if your liver or kidneys are not working properly
- if you have had or you 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. As trastuzumab may affect the heart, you should not use Pharmorubicin for up to 7 months after you have stopped taking trastuzumab. If Pharmorubicin is used before this time, then your heart function should be carefully monitored.
- in pregnant women, there have been a few reports that Pharmorubicin has been associated with heart problems in new-borns and unborn babies, including foetal death.

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

Other medicines and Pharmorubicin:
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 Pharmorubicin 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 pharmorubicin for up to 7 months after stopping trastuzumab when possible. If pharmorubicin is used before this time, careful monitoring of cardiac function is recommended
- **Vaccination** with a live vaccine should be avoided in patients receiving epirubicin
- **Paclitaxel or docetaxel** (drugs used to treat cancer). When paclitaxel is given prior to epirubicin, it may increase concentration of epirubicin in blood. However when paclitaxel and docetaxel are given together and given after epirubicin, they did not affect concentration of epirubicin
- **Dexverapamil** (used to treat some heart conditions)
- **Dexrazoxane** (used to prevent chronic cumulative cardiotoxicity caused by epirubicin)
- **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 Pharmorubicin 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 Pharmorubicin and 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 Pharmorubicin 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: Pharmorubicin 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 Pharmorubicin 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.

Pharmorubicin 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.

Pharmorubicin contains sodium
Pharmorubicin 10 mg/5 ml (2 mg/ml) solution for injection or infusion contains 17.7 mg of sodium (main component of cooking/table salt) in each 5 ml vial. This is equivalent to 0.9% of the recommended maximum daily dietary intake of sodium for an adult.

Pharmorubicin 50 mg/25 ml (2 mg/ml) solution for injection or infusion contains 88.5 mg sodium (main component of cooking/table salt) in 25 ml vial. This is equivalent to 4.4% of the recommended maximum daily dietary intake of sodium for an adult.

Pharmorubicin 200 mg/100 ml (2 mg/ml) solution for injection or infusion contains 354 mg sodium (main component of cooking/table salt) in 100 ml vial. This is equivalent to 17.7% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pharmorubicin

If you are prescribed Pharmorubicin it will only 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 on your condition.

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

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

If you 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
- 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 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
- Skin changes
- Abnormal discolouration of skin
- 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 col 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 and pain in the legs or arms due to inflammation of a blood vessel, possibly including blood clotting
- 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 Pharmorubicin

- The unopened vials should be stored in the original container in order to protect from light until ready for use. Store at 2°C to 8°C (in a refrigerator).
- Storage of the solution for injection or infusion at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after 2 to a maximum of 4 hours equilibration at controlled room temperature (15-25ºC). Solution for injection or infusion should be used within 24 hours after removal from refrigeration.
- Keep out of the sight and reach of children.
- This medicine should not be used after the expiry date printed on the box and on the 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.

6. Contents of the pack and other information

What Pharmorubicin contains
The active substance is epirubicin hydrochloride. The other ingredients are hydrochloric acid, sodium chloride (see section 2 “Pharmorubicin contains sodium”) and water for injections.

What Pharmorubicin looks like and contents of the pack

Pharmorubicin is a red solution for injection or infusion containing 10 mg, 50 mg or 200 mg of epirubicin hydrochloride as a 2 mg/ml solution in single glass vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Pfizer Limited

Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK

Manufacturer: Pfizer Service Company BV,
10 Hoge Wei, 1930 Zaventem,
Belgium.

Company contact address:
For further information please contact Medical Information at Pfizer Limited in Walton Oaks, Tadworth, Surrey, KT20 7NS. Tel: 01304 616161.

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A GUIDE FOR HOSPITAL STAFF

Pharmorubicin® 2 mg/ml Solution for Injection or Infusion
Solution for Injection or Infusion
epirubicin hydrochloride

Pfizer Logo

IMPORTANT: Refer to Summary of Product Characteristics before prescribing.

Presentation:
Sterile, red, mobile solution containing 10 mg, 50 mg and 200 mg of epirubicin hydrochloride as a 2 mg/ml solution in 0.9% sodium chloride solution.

Uses:
Pharmorubicin 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 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:
Pharmorubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

Pharmorubicin solution should be administered only under the supervision of a qualified physician experienced in antiblastic and cytotoxic therapy. Treatment with high dose Pharmorubicin 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 Pharmorubicin 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 Pharmorubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m² 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 neutropaenia/neutropaenic 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:

Pharmorubicin 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): 120 mg/m² day 1, every 3 weeks.
- non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m² day 1 or 45 mg/m² 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 ranging from 100 mg/m² (as a single dose on day 1) to 120 mg/m² (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 (60-75 mg/m² for conventional treatment and 105-120 mg/m² 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 Pharmorubicin 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: 1.4-3 mg/100 ml) requires a 50% reduction of dose, while severe impairment (bilirubin >3 mg/100 ml) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Pharmorubicin excreted by this route.

Intravesical administration:
Pharmorubicin 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 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 50 mg/50 ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50 ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg/50 ml. For prophylaxis, 4 x weekly administrations of 50 mg/50 ml 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 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 generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin (e.g., ≥ 90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/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 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 in excess of 900 mg/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 and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin 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. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as epirubicin 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 traztuzumab 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 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 (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 may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, 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.

Gastrointestinal **-** Epirubicin is emetigenic. 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 is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. Lower doses of epirubicin 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 >5 mg/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 minimize the risk of phlebitis/thrombophlebitis at the injection site (see section **4.2**).

Extravasation **-** Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. The adverse effect of extravastation 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.

Tumour-lysis syndrome **-** Epirubicin 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, may result in serious or fatal infections (see section **4.5**). Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Reproductive system **-** Epirubicin can cause genotoxicity. Men and women treated with epirubicin should adopt appropriate contraceptives during and for a period after treatment with epirubicin (see section **4.6**).

Intravesical administration of epirubicin 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 (transcatheter arterial embolization for the localized 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) localized or regional events which include gastro-duodenal 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 is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see section **4.4**). The use of epirubicin 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 is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section **4.4**).

Anthracyclines including epirubicin 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. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Cimetidine increased the AUC of epirubicin by 50% and should be discontinued during treatment with epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin 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 with the following frequencies:

System Organ Class	**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**	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations	Infection, Conjunctivitis		Sepsis*, Pneumonia*			
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Acute myeloid leukaemia, Acute lymphocytic leukaemia			
Blood and lymphatic system disorders	Anaemia, Leukopenia, Neutropenia, Thrombocytopenia Febrile neutropenia					

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
Immune system disorders				Anaphylactic reaction*		
Metabolism and nutrition disorders		Decreased appetite Dehydration*		Hyperuricaemia*		
Eye disorders	Keratitis					
Cardiac disorders		Ventricular tachycardia, Atrioventricular block, Bundle branch block, Bradycardia, Cardiac failure congestive				
Vascular disorders	Hot flush, Phlebitis*	Haemorrhage*, Flushing*	Embolism, Embolism arterial*, Thrombophlebitis*			Shock*
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			
Gastrointestinal disorders	Nausea, Vomiting, Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain*, Gastrointestinal erosion*, Gastrointestinal ulcer*	Gastrointestinal haemorrhage*			Abdominal discomfort, Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia, Skin toxicity	Rash/Pruritus, Nail pigmentation*, Skin disorder, Skin hyperpigmentation*	Urticaria* Erythema*			Photosensitivity reaction*
Renal and urinary disorders	Chromaturia*†					
Reproductive system and breast disorders	Amenorrhoea					
General disorders	Malaise, Pyrexia*	Chills*	Asthenia			

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
and administration site conditions						
Investigations	Transaminases abnormal	Ejection fraction decreased				
Injury, poisoning and procedural complications	Chemical cystitis*§					Recall phenomenon*Δ

* ADR identified post-marketing.
† Red coloration 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 the Yellow Card Scheme at 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 in pregnant women. Studies in animals have shown reproductive toxicity (see section **5.3**).

Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman. Avoid the use of epirubicin 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 during the 2nd and 3rd trimesters.

If epirubicin 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 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 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 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, lactating women should be advised not to breast-feed during treatment with epirubicin and for at least 7 days after last dose.

Impairment of fertility
Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy.

Epirubicin may cause amenorrhoea or premature menopause in premenopausal women.

Women of childbearing potential/ Contraception in males and females
Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6.5 months after last dose.

Men undergoing treatment with epirubicin should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.

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 will result in severe myelosuppression (mainly leucopoenia 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 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 handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling Pharmorubicin Solution should wear protective clothing: goggles, gowns, and disposable gloves and masks.
- All items used for 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. Pharmorubicin should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

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

Shelf life

Glass vials – three years from time of manufacture.

Storage

The vials should be stored at between 2°C - 8°C (in the refrigerator).
Keep the vial in the outer carton in order to protect from light.

Storage of the solution for injection or infusion at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after 2 to a maximum of 4 hours equilibration at controlled room temperature (15-25ºC). Solution for injection or infusion should be used within 24 hours after removal from refrigeration.

Shelf life after first opening the container

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 are the responsibility of the user.
Vials are for single use only and any unused portion must be discarded after use.

Package quantities:
10 mg, 50 mg and 200 mg vials for intravenous or intravesicular use.

POM

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This leaflet was prepared in 12/2023.

Further information is available to the medical and allied professions on request from:
Medical Information at Pfizer Limited, Walton Oaks, Tadworth, Surrey, KT20 7NS, UK.
Tel: 01304 616161.