Epirubicin Hydrochloride Injection I.P. and Epirubicin Hydrochloride for Injection

FARMORUBICIN®

Ready-to-use solution for injection and Rapid dissolution powder for injection

1. GENERIC NAME

Epirubicin Hydrochloride Rapid dissolution (Powder for injection)
Epirubicin Hydrochloride Ready-to-use (Solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: Epirubicin hydrochloride I.P.

Epirubicin hydrochloride is available as:

Rapid dissolution freeze dried powder for solution for injection containing 10 mg and 50 mg Epirubicin Hydrochloride I.P.

(Each 10 mg vial of epirubicin hydrochloride is accompanied by an ampoule containing 5 mL of Water for Injections.
Each 50 mg vial of epirubicin hydrochloride is to be dissolved in 25 mL of physiological saline.)

Solution for injection in vials containing10 mg and 50 mg of Epirubicin Hydrochloride I.P. (strength 2 mg/mL) as a ready-to-use solution.

Epirubicin 10 mg/5 ml powder and solvent for solution for infusion contains 17.7 mg of sodium in each 5 ml vial.

List of Excipients

Freeze Dried Powder:

- Methyl p-hydroxybenzoate.
- Lactose (as lactose anhydrous).

® Trademark Proprietor: Pfizer Italia SRL
Licensed User: Pfizer Products India Private Limited, India

Solution for Injection:
Sodium Chloride, Hydrochloric Acid, Water For Injections

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Sterile powder for solution for injection 10 mg and 50 mg

Sterile solution for injection 10 mg/5 ml and 50 mg/25 ml

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

- Breast carcinoma
- Gastric carcinoma
- Head and neck carcinoma
- Hepatic carcinoma
- Leukemia
- Lung carcinoma
- Malignant lymphomas
- Ovarian carcinoma
- Pancreatic carcinoma
- Sigmoido-Rectal carcinoma
- Soft-tissue sarcomas

4.2 Posology and method of administration

Posology

Intravenous administration

Dosage plan for standard doses

When Epirubicin is used as the sole antiblastic agent, the recommended dose for adults is 60-90 mg/m² of body surface area, to be administered by intravenous injection over 5-10 minutes at intervals of 21 days, compatibly with blood/bone marrow conditions.

Dosage plan for high doses

Carcinoma of the lung
When used as a single agent at high doses in the treatment of pulmonary carcinoma, Epirubicin should be administered according to the following regimens:
small cell lung cancer in previously untreated patients: 120 mg/m² on day 1, every three weeks.

non small cell lung cancer (epidermoid, squamous and adenocarcinoma) in previously untreated patients: 135 mg/m² on day 1 or 45 mg/m² on Days 1,2,3, every three weeks.

Carcinoma of the breast
Doses of up to 135 mg/m², when used as the sole agent, and up to 120 mg/m² when used in combination therapy, administered every 3-4 weeks, have been found to be effective and well tolerated in patients suffering from carcinoma of the breast.

In adjuvant treatment of mammary carcinoma in the initial stages, the recommended doses vary from 100 mg/m² to 120 mg/m² administered every 3-4 weeks.

The drug should be administered by intravenous bolus injection over 5-10 minutes or as an intravenous infusion over a maximum of 30 minutes.

Lower doses (60-75 mg/m² or 105-120 mg/m² in the dosage plans for high doses) are recommended for patients with diminished bone marrow reserves due to previous treatment with chemotherapy and/or radiotherapy, old age, or neoplastic bone marrow infiltration. The total dose per cycle can be divided up over 2-3 consecutive days.

If used in combination therapy with other anti-neoplastic agents, the doses should be suitably reduced.

Since the main route of elimination of the drug is via the hepato-biliary system, it is suggested that the dosage of Epirubicin be reduced in patients with impaired liver function, so as to avoid an increase in global toxicity.

Generally speaking, when the bilirubin levels are between 1.4-3 mg/100 ml, and the retention of bromosulfophthalein (BSP) is 9-15%, it is recommended that half the normal dose of the drug be administered.

If the bilirubin levels and the BSP retention levels are even higher than that, it is recommended that a quarter of the normal dose be administered.

Moderate impairment of renal function does not appear to be a sufficient reason for altering the recommended doses, because of the low level of excretion of Epirubicin through the kidneys.

Method of administration

Epirubicin is not active if taken orally and it should not be administered either intramuscularly or intrathecally.

Intravenous administration

Intravenous administration should be carried out over a period of 5-10 minutes via the tubing of an intravenous infusion of normal saline solution already in situ, after checking that the

needle is perfectly inserted in the vein. This technique reduces the risk of perivenous extravasation and ensures that the vein is washed through at the end of administration.

If Epirubicin leaks from the vein during administration, there can be tissue damage which may even result in necrosis.

Venous sclerosis may be observed when the injection is carried out in small blood vessels or repeated into the same vein.

Preparation of the solution
Intravenous use:

Epirubicin dissolves completely in either water or normal saline solution. The latter is to be preferred because an isotonic solution is thus obtained, which is known to be better tolerated.

Vials of lyophilized powder	Quantity of diluent to be added	Final concentration
10 mg	5 ml	2 mg/ml
50 mg	25 ml	2 mg/ml

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 2, other anthracyclines or anthracenediones.

- Lactation.

Intravenous use:
- Persistent myelosuppression.
- Severe hepatic impairment.
- Myocardiopathy.
- Recent myocardial infarction.
- Severe arrhythmias.
- Previous treatments with maximum cumulative doses of epirubicin hydrochloride and/or other anthracyclines and anthracenediones (see section **4.4 Special warnings and precautions for use**).
- Patients with acute systemic infections.
- Unstable angina pectoris.

4.4 Special warnings and precautions for use

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 generalized infections) of prior cytotoxic treatment before beginning

treatment with epirubicin hydrochloride.

While treatment with high doses of epirubicin hydrochloride (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/mucositis may be increased. Treatment with high doses of the drug 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.

Early (i.e., Acute) Events. Early cardiotoxicity of epirubicin hydrochloride consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities, such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin hydrochloride treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin hydrochloride or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF), such as dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm.

Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin hydrochloride 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.

The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography. A baseline cardiac evaluation with an ECG and either a MUGA scan or an echocardiography is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher,

cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin hydrochloride should be exceeded only with extreme caution.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section **4.5 Drugs interactions**) with an increased risk in the elderly.

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 trastuzumab and anthracyclines.

Because the reported half-life of trastuzumab is approximately 4-5 (28 to 38 days) weeks, trastuzumab may persist in the circulation for up to 20-27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin are used, 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.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

Hematologic Toxicity **-** As with other cytotoxic agents, epirubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug.

Leukopenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21.

Thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia **-** Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1-to 3-year latency period (see section **5.1 Pharmacodynamic properties**, ***Clinical Studies***).

Gastrointestinal **-** Epirubicin hydrochloride is emesis. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

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. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see sections **4.2 Posology and method of administration** and **5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations**). Patients with severe hepatic impairment should not receive epirubicin hydrochloride (see section **4.3 Contraindications**).

Renal Function - Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine >5 mg/dl (see section **4.2 Posology and method of administration**).

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 Posology and method of administration**).

Extravasation - Extravasation of epirubicin hydrochloride during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin hydrochloride, the drug infusion should be immediately discontinued. 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.

The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

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.

Tumor-Lysis Syndrome - Epirubicin may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections - Administration of use or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin hydrochloride, may result in serious or fatal infections (see section **4.5 Drugs interactions**). 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. Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

Epirubicin, powder for solution for injection, contains methyl parahydroxybenzoate. This may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

Epirubicin 10 mg/5 ml (2 mg/ml) contains 17.7 mg of sodium in each 5 ml vial, equivalent to 0.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Drugs interactions

Epirubicin hydrochloride may also be used in combination with other anti-neoplastic agents in chemotherapy. Additive toxicity may occur especially with regard to bone marrow/hematologic and gastro-intestinal effects (see section **4.4 Special warnings and precautions for use**). 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 metabolized 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 Special warnings and precautions for use**).

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section **4.5 Drugs interactions**). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. lf anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

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. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin hydrochloride when epirubicin hydrochloride was administered prior to the taxane.

This combination may be used if using staggered administration between the two agents. Infusion of epirubicin hydrochloride and paclitaxel should be performed with at least a 24 hours interval between the 2 agents.

Dexverapamil may alter the pharmacokinetics of epirubicin hydrochloride and possibly increase its bone marrow depressant effects.

One study found that docetaxel may increase the plasma concentrations of epirubicin hydrochloride metabolites when administered immediately after epirubicin hydrochloride.

Quinine may accelerate the initial distribution of epirubicin hydrochloride from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin hydrochloride.

The co-administration of interferon α2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin hydrochloride.

The possibility of a marked disturbance of hematopoiesis needs to be kept in mind with a (pre)treatment with medications which influences the bone marrow (i.e. cytostatic agents, sulphonamide chloramphenicol diphenylhydantoin, amidopyrine-derivate. antiretroviral agents).

Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

4.6 Use in special populations

Fertility

Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with Epirubicin should use effective contraceptive methods and if appropriate and available, seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy.

Epirubicin may cause amenorrhea or premature menopause in pre-menopausal women.

Pregnancy

Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods.

Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman. 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 fetus.

There are no studies in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

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, mothers should discontinue nursing prior to taking this drug.

4.7 Effects on ability to drive and use machines

Epirubicin has not any effects on the ability to drive or to use machinery.

4.8 Undesirable effects

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

More than 10% of treated patients can expect to develop undesirable effects. The most common undesirable effects are mye1osuppression, gastrointestinal side effects anorexia, alopecia, infection.

System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100, <1/10)**	**Uncommon (≥ 1/1.000, < 1/100)**	**Rare (≥ 1/10.000, < 1/1.000)**	**Very rare (< 1/10.000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection, Conjunctivitis		Sepsis* Pneumonia*			Septic shock, Cellulitis
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)			Acute lymphocytic leukaemia, acute myelogenous leukaemia			
Blood and the lymphatic system disorders	Myelosuppression (leukopenia, granulocytopenia and neutropenia, anaemia, thrombocytopenia, febrile					

	neutropenia)					
Immune system disorders				Hypersensitivity[§], anaphylactic reaction[*]		
Metabolism and nutrition disorders		Reduced appetite, Dehydration[*]		Hyperuricemia[*]		
Nervous system disorders		Burning sensation[§]		Dizziness		
Eye disorders	Keratitis					
Cardiac disorders		Congestive heart failure[^], ventricular tachycardia, bradycardia, AV block, branch block		Cardiotoxicity[‖]		
Vascular disorders	Hot flushes, phlebitis[*]	Haemorrhage[*], flushes[*]	Embolism[*], arterial embolism[*], thrombophlebitis[*]			Shock[*]
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism[*]			Hypoxia[ω]

Gastrointestinal disorders	Nausea, vomiting, stomatitis, mucosal inflammation, diarrhoea	Gastrointestinal pain*, gastrointestinal erosion*, oesophagitis, gastrointestinal ulcer*	Gastrointestinal haemorrhage*			Abdominal discomfort, erosion of oral mucosa, mouth ulcers, oral pain, burning sensation in mucosa, oral haemorrhage, buccal pigmentation*
Skin and subcutaneous disorders	Alopecia, skin toxicity	Rash/pruritus, nail pigmentation*, skin changes, skin hyperpigmentation*	Urticaria* Erythema*			Photosensitivity*
Renal and urinary disorders	Chromaturia*†	Pollakiuria§				
Reproductive system and breast disorders	Amenorrhoea			Azoospermia		
General disorders and administration site conditi	General malaise*, pyrexia*	Erythema at infusion site, chills*	Asthenia			Phlebosclerosis, pain, soft tissue necrosisε

ons						
Investigations	Abnormal transaminase levels	Reduced ejection fraction rate				
Injury, poisoning and procedural complications	Chemical cystitis[*§]					Recall phenomenon[*Δ]

[*] Post-marketing undesirable effects
[ω] induced by myelosuppression
[^] (dyspnoea, oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusion, racing heartbeat)
[‖] e.g., change in ECG, arrhythmia, cardiomyopathy
[†] Red coloration of urine for 1 to 2 days after administration
[ε] following accidental paravenous injection
[§] after intravenous administration (see paragraph **4.4 "Special warnings and precautions for use"**)
[Δ] hypersensitivity of previously irradiated skin

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.

4.9 Overdose

Acute overdosage with epirubicin hydrochloride will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications.

Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section **4.4 Special warnings and precautions for use**). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment of the symptomatic overdosage: Epirubicin hydrochloride cannot be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Epirubicin is an anthracycline cytotoxic agent. Although it is known that anthracyclines can interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of epirubicin's cytotoxic and/or antiproliferative properties have not been completely elucidated.

Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms.

Epirubicin is cytotoxic *in vitro* to a variety of established murine and human cell lines and primary cultures of human tumors. It is also active *in vivo* against a variety of murine tumors and human xenografts in athymic mice, including breast tumors.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics, anthracyclines – ATC code: L01DB03

Epirubicin hydrochloride has been found to be active on a wide spectrum of experimental tumours, in particular leukaemias (LK 1210, P 388), sarcomas (SA 180 solid and ascitic), melanoma (B 16), carcinoma of the breast, Lewis pulmonary carcinoma, carcinoma of the colon (38) and also on human tumours transplanted into athymic mice (melanoma, carcinoma of the mammary glands, the lungs, the prostate and the ovaries).

Clinical Studies

Adjuvant Treatment of Patients with Early Breast Cancer

Two randomized, open-label, multicenter studies evaluated the use of epirubicin 100 to 120 mg/m^2 in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m^2 of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized pre-menopausal and peri-menopausal women with one or more positive lymph nodes to an epirubicin-containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m^2 of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100). This study randomized pre- and post-menopausal women to the FEC-100 regimen or to a lower-dose FEC-50 regimen. In the

GFEA-05 study, eligible patients were either required to have ≥4 nodes involved with tumor or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptors and a histologic tumor grade of 2 or 3. A total of 1281 women participated in these studies. Patients with T4 tumors were not eligible for either study.

Table 1 shows the treatment regimens that the patients received. The primary endpoint of the trials was relapse-free survival, i.e., time to occurrence of a local, regional, or distant recurrence, or disease-related death. Patients with contralateral breast cancer, second primary malignancy or death from causes other than breast cancer were censored at the time of the last visit prior to these events.

Table 1. Treatment Regimens Used in Phase 3 Studies of Patients with Early Breast Cancer

	Treatment Groups	Agent	Regimen
MA-5[1] N=716	**CEF-120** (total, 6 cycles)[2] N=356	Cyclophosphamide Epirubicin Fluorouracil	75 mg/m^2 PO, d 1-14, q 28 days 60 mg/m^2 IV, d 1 & 8, q 28 days 500 mg/m^2 IV, d 1 & 8, q 28 days
	CMF (total, 6 cycles) N=360	Cyclophosphamide Methotrexate Fluorouracil	100 mg/m^2 PO, d 1-14, q 28 days 40 mg/m^2 IV, d 1 & 8, q 28 days 600 mg/m^2 IV, d 1 & 8, q 28 days
GFEA-05[3] N=565	**FEC-100** (total, 6 cycles) N=276	Fluorouracil Epirubicin Cyclophosphamide	500 mg/m^2 IV, d 1, q 21 days 100 mg/m^2 IV, d 1, q 21 days 500 mg/m^2 IV, d 1, q 21 days
	FEC-50 (total, 6 cycles) N=289	Fluorouracil Epirubicin Cyclophosphamide	500 mg/m^2 IV, d 1, q 21 days 50 mg/m^2 IV, d 1, q 21 days 500 mg/m^2 IV, d 1, q 21 days
	Tamoxifen 30 mg daily x 3 years, post-menopausal women, any receptor status		

[1] In women who underwent lumpectomy, breast irradiation was to be administered after completion of study chemotherapy.
[2] Patients also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or fluoroquinolone for the duration of their chemotherapy.
[3] All women were to receive breast irradiation after the completion of chemotherapy.

In the MA-5 trial, the median age of the study population was 45 years. Approximately 60% of patients had 1 to 3 involved nodes and approximately 40% had ≥4 nodes involved with tumor. In the GFEA-05 study, the median age was 51 years and approximately half of the patients were post-menopausal. About 17% of the study population had 1 to 3 positive nodes and 80% of patients had ≥4 involved lymph nodes. Demographic and tumor characteristics were well-balanced between treatment arms in each study.

The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results for endpoints were initially analyzed after up to 5 years of follow-up and these results are presented in the text below and in Table 2. Results after up to 10 years of follow-up are presented in Table 2. In Study MA-5, epirubicin-containing combination therapy (CEF-120) showed significantly longer RFS than CMF (5-year estimates were 62% versus

53%, stratified log-rank for the overall RFS p = 0.013). The estimated reduction in the risk of relapse was 24% at 5 years. The OS was also greater for the epirubicin-containing CEF-120 regimen than for the CMF regimen (5-year estimate 77% versus 70%; stratified log-rank for overall survival p = 0.043; non-stratified log-rank p = 0.13). The estimated reduction in the risk of death was 29% at 5 years.

In Study GFEA-05, patients treated with the higher-dose epirubicin regimen (FEC-100) had a significantly longer 5-year RFS (estimated 65% versus 52%, log-rank for the overall RFS p = 0.007) and OS (estimated 76% versus 65%, log-rank for the overall survival p = 0.007) than patients given the lower dose regimen (FEC-50). The estimated reduction in risk of relapse was 32% at 5 years. The estimated reduction in the risk of death was 31% at 5 years. Results of follow-up up to 10 years (median follow-up = 8.8 years and 8.3 years, respectively, for Study MA-5 and Study GFEA-05) are presented in Table 2.

Although the trials were not powered for subgroup analyses, in the MA-5 study, improvements in favor of CEF-120 vs. CMF were observed, in RFS and OS both in patients with 1-3 node positive and in those with ≥4 node positive tumor involvement. In the GFEA-05 study, improvements in RFS and OS were observed in both pre- and post-menopausal women treated with FEC-100 compared to FEC-50.

Table 2. Efficacy Results from Phase 3 Studies of Patients with Early Breast Cancer*

	MA-5 Study		GFEA-05 Study	
	CEF-120 N=356	CMF N=360	FEC-100 N=276	FEC-50 N=289
RFS at 5 yrs (%)	62	53	65	52
Hazard ratio†	0.76		0.68	
2-sided 95% CI	(0.60, 0.96)		(0.52, 0.89)	
Log-rank test stratified**	(p = 0.013)		(p = 0.007)	
OS at 5 yrs (%)	77	70	76	65
Hazard ratio†	0.71		0.69	
2-sided 95% CI	(0.52, 0.98)		(0.51, 0.92)	
Log-rank test stratified**	(p = 0.043) (unstratified p = 0.13)		(p = 0.007)	
RFS at 10 yrs (%)	51	44	49	43
Hazard ratio†	0.78		0.78	
2-sided 95% CI	(0.63, 0.95)		(0.62, 0.99)	
Log-rank test stratified**	(p = 0.017) (unstratified p = 0.023)		(p = 0.040) (unstratified p = 0.09)	
OS at 10 yrs (%)	61	57	56	50
Hazard ratio†	0.82		0.75	
2-sided 95% CI	(0.65, 1.04)		(0.58, 0.96)	
Log-rank test stratified**	(p = 0.100) (unstratified p = 0.18)		(p = 0.023) (unstratified p = 0.039)	

*Based on Kaplan-Meier estimates.
**Patients in MA-5 were stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by hormone receptor status (ER or PR positive (≥10 fmol), both negative (<10 fmol), or unknown status). Patients in GFEA-05 were stratified by nodal status (1-3, 4-10, and >10 positive nodes).

†Hazard ratio: CMF:CEF-120 in MA-5, FEC-50:FEC-100 in GFEA-05.

The Kaplan-Meier curves for RFS and OS from Study MA-5 are shown in Figures 1 and 2 and those for Study GFEA-05 are shown in Figures 3 and 4.

Figure 1. Relapse-free Survival in Study MA-5

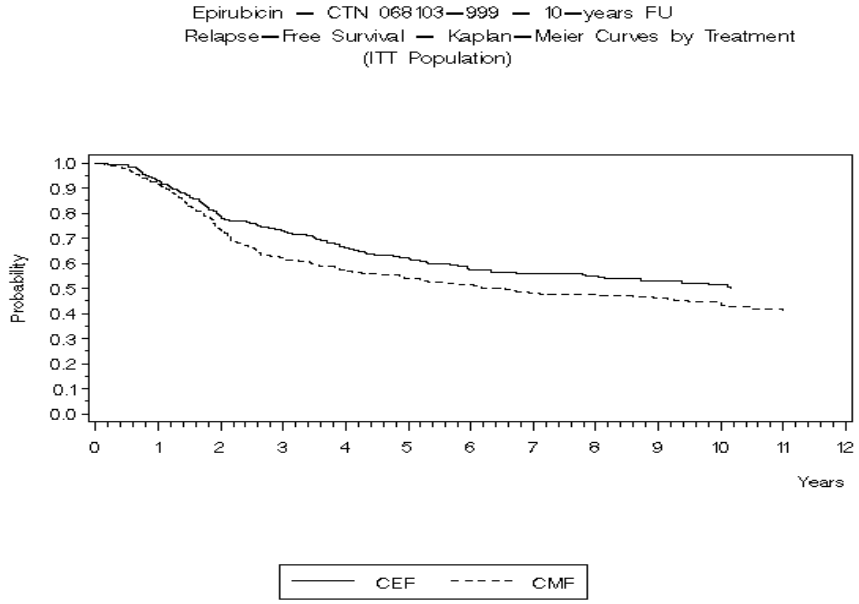


Figure 2. Overall Survival in Study MA-5

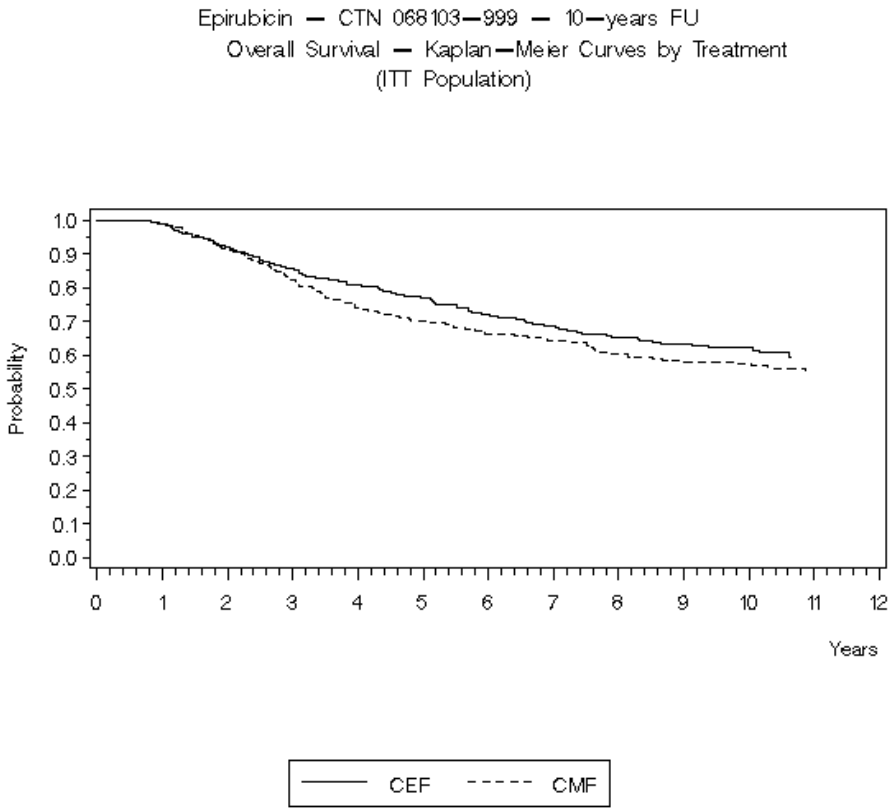


Figure 3. Relapse-free Survival in Study GFEA-05

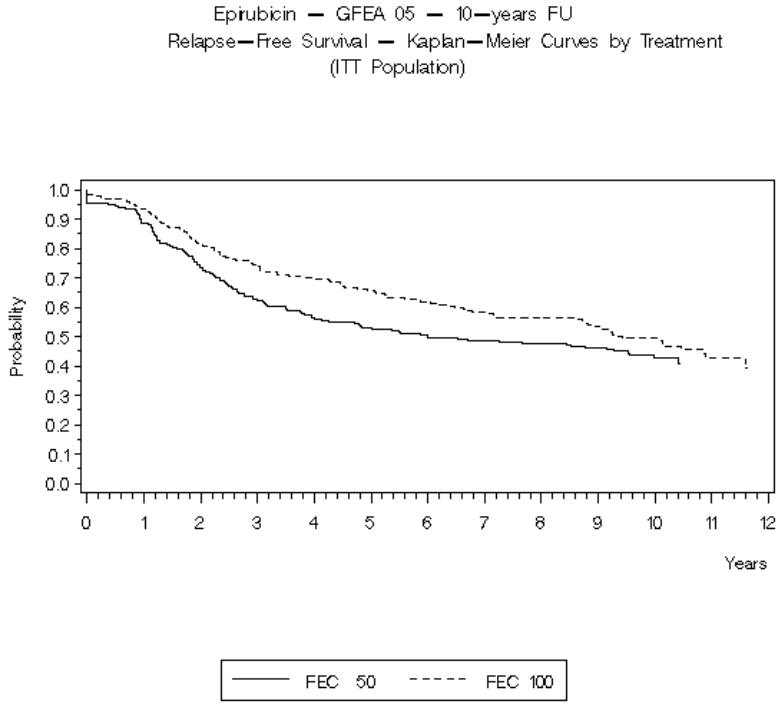
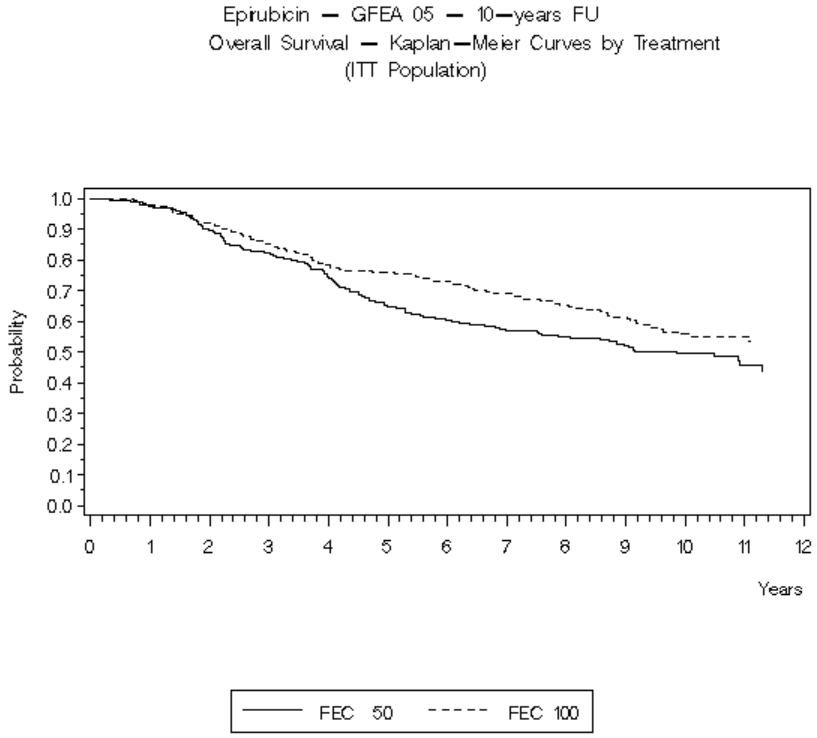


Figure 4. Overall Survival in Study GFEA-05

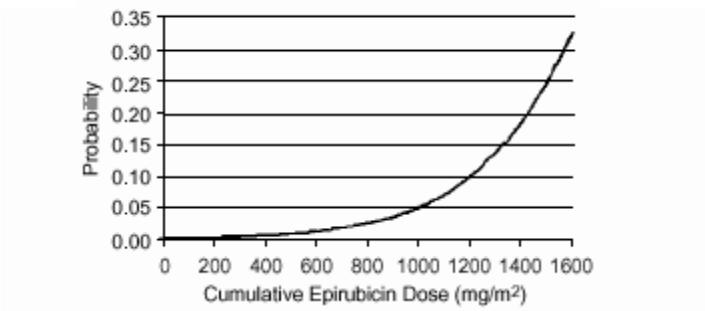


See Table 2 for statistics on 5 and 10 year analyses.

Cardiac Function

In a retrospective survey, including 9144 patients, mostly with solid tumors in advanced stages, the probability of developing CHF increased with increasing cumulative doses of epirubicin (Figure 5). The estimated risk of epirubicin-treated patients developing clinically evident CHF was 0.9% at a cumulative dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF in the absence of other cardiac risk factors increased steeply after an epirubicin cumulative dose of 900 mg/m^2.

Figure 5. Risk of CHF in 9144 Patients Treated with Epirubicin

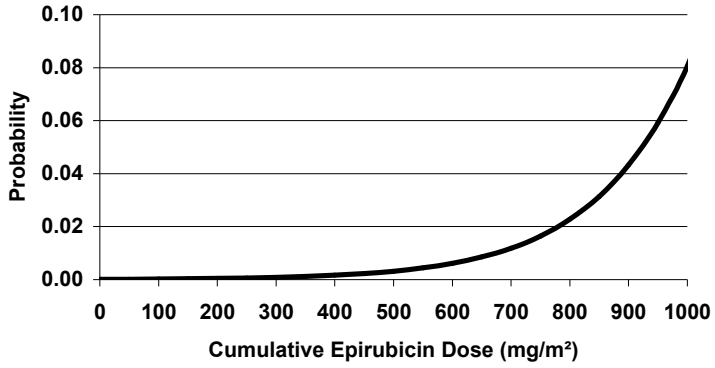


In another retrospective survey of 469 epirubicin-treated patients with metastatic or early breast cancer, the reported risk of CHF was comparable to that observed in the larger study of over 9000 patients.

Secondary Leukemia

An analysis of 7110 patients who received adjuvant treatment with epirubicin in controlled clinical trials as a component of poly-chemotherapy regimens for early breast cancer, showed a cumulative risk of secondary acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) of about 0.27% (approximate 95% CI, 0.14-0.40) at 3 years, 0.46% (approximate 95% CI, 0.28-0.65) at 5 years and 0.55% (approximate 95% CI, 0.33-0.78) at 8 years. The risk of developing AML/MDS increased with increasing epirubicin cumulative doses as shown in Figure 6.

Figure 6. Risk of AML/MDS in 7110 Patients Treated with Epirubicin



AML/MDS rates increased with epirubicin dose per cycle, and cumulative dose. For instance, in the MA-5 trial, in patients that received intensive doses of epirubicin (120 mg/m^2), the incidence of AML/MDS was 1.1% at 5 years with no additional cases observed during the second 5 years (years 6-10) of follow-up.

The cumulative probability of developing AML/MDS was found to be particularly increased in patients who received more than the maximum recommended cumulative dose of epirubicin (720 mg/m^2) or cyclophosphamide (6,300 mg/m^2), as shown in Table 3.

Table 3. Cumulative Probability of AML/MDS in Relation to Cumulative Doses of Epirubicin and Cyclophosphamide

Years from Treatment Start	Cumulative Probability of Developing AML/MDS % (95% CI)			
	Cyclophosphamide Cumulative Dose ≤6,300 mg/m^2		Cyclophosphamide Cumulative Dose >6,300 mg/m^2	
	Epirubicin Cumulative Dose ≤720 mg/m^2 N=4760	Epirubicin Cumulative Dose >720 mg/m^2 N=111	Epirubicin Cumulative Dose ≤720 mg/m^2 N=890	Epirubicin Cumulative Dose >720 mg/m^2 N=261
3	0.12 (0.01-0.22)	0.00 (0.00-0.00)	0.12 (0.00-0.37)	4.37 (1.69-7.05)
5	0.25 (0.08-0.42)	2. 38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)

8	0.37 (0.13-0.61)	2. 38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)

5.3 Pharmacokinetic properties

Epirubicin pharmacokinetics are linear over the dose range of 60 to 150 mg/m^2 and plasma clearance is not affected by the duration of infusion or administration schedule.

Distribution. Following intravenous administration, epirubicin is rapidly and widely distributed into the tissues. Binding of epirubicin to plasma proteins, predominantly albumin, is about 77% and is not affected by drug concentration. Epirubicin also appears to concentrate in red blood cells; whole blood concentrations are approximately twice those of plasma.

Metabolism. Epirubicin is extensively and rapidly metabolized by the liver and is also metabolized by other organs and cells, including red blood cells. Four main metabolic routes have been identified:

(1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative, epirubicinol;
(2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid;
(3) loss of the amino sugar moiety through a hydrolytic process with the formation of the doxorubicin and doxorubicinol aglycones; and
(4) loss of the amino sugar moiety through a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-doxorubicinol aglycone. Epirubicinol has *in vitro* cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug, they are unlikely to reach *in vivo* concentrations sufficient for cytotoxicity. No significant activity or toxicity has been reported for the other metabolites.

Excretion. Epirubicin and its major metabolites are eliminated through biliary excretion and, to a lesser extent, by urinary excretion. Mass-balance data from 1 patient found about 60% of the total radioactive dose in feces (34%) and urine (27%). These data are consistent with those from 3 patients with extrahepatic obstruction and percutaneous drainage, in whom approximately 35% and 20% of the administered dose were recovered as epirubicin or its major metabolites in bile and urine, respectively, in the 4 days after treatment.

Pharmacokinetics in Special Populations

Hepatic Impairment. Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups. Patients in Group 1 (n = 22) had serum AST (SGOT) levels above the upper limit of normal (median: 93 IU/L) and normal serum bilirubin levels (median: 0.5 mg/dL) and were given epirubicin doses of 12.5 to 90 mg/m^2. Patients in Group 2 had alterations in both serum AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an epirubicin dose of 25 mg/m^2 (n = 8). Their pharmacokinetics were compared to those of patients with normal serum AST and bilirubin values, who received epirubicin doses of 12.5 to 120 mg/m^2. The median plasma clearance of epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated (see sections **4.2 Posology and method of administration** and **4.4 Special warnings and precautions for use**).

Renal Impairment. No significant alterations in the pharmacokinetics of epirubicin or its major metabolite, epirubicinol, have been observed in patients with serum creatinine <5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine ≥5 mg/dL (see sections **4.2 Posology and method of administration** and **4.4 Special warnings and precautions for use**). Patients on dialysis have not been studied.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

The LD50 of epirubicin hydrochloride in mice and rats was, respectively, 29.3 and 14.2 mg/Kg and approximately 2.0 mg/Kg in dogs. Studies regarding toxicity with repeated administrations (rabbits and dogs) and cardiotoxicity (rats and rabbits) have demonstrated that epirubicin hydrochloride is characterized by a lower degree of toxicity than doxorubicin. Epirubicin hydrochloride has demonstrated mutagenic and carcinogenic properties in experimental animals.

7. DESCRIPTION

Freeze Dried powder: Porous, red, freeze-dried cake or mass.

Solution for Injection: Clear and clean red solution

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

- Epirubicin should not be mixed with other drugs.
- Contact with any solution of an alkaline pH should be avoided, as it will result in hydrolysis of the drug.

- Epirubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

8.2 Shelf-life

Rapid dissolution powder for injection:
48 months

Ready-to-use solution for injection:
36 months

8.3 Packaging information

Freeze Dried Powder:

- 10 mg vials (Type – 1 glass vials) containing 10 mg epirubicin hydrochloride as freeze dried powder with a solvent ampoule containing 5 mL of water for injection.
- 50 mg vials (Type – 1 glass vials) containing 50 mg epirubicin hydrochloride as freeze dried powder.

Solution for Injection:

- Epirubicin Hydrochloride Injection 2 mg/mL is contained in vials of 5 mL (10 mg) and 25 mL (50 mg) nominal capacity manufactured from medical-grade polypropylene resin. The vials are closed with siliconised, halobutyl rubber stoppers (Teflon or FluroTec Plus-faced) and sealed with aluminium crimps (or caps) with plastic, flip-off tops printed with the words "Cytotoxic – Dispose of Properly".

8.4 Storage and handling instructions

Freeze Dried Powder:

- Store between 15ºC and 30ºC.
- Protected from light
- Keep out of reach of Children

Solution for Injection:

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

- Store at 2ºC to 8ºC. Do not Freeze.

Instructions for Use/Handling and Disposal

Reconstitution of the freeze-dried powder for intravenous administration

- Dissolve in sodium chloride/water for injection as indicated below:

Freeze-dried vial	Diluent added	Final concentration

10 mg	5 mL	2 mg/mL
50 mg	25 mL	2 mg/mL

Discard the solution if content is not clear or if particulate matter or discolouration is observed.

Instructions for the ampoule opening

Attention: New type of ampoule (one point cut)

To open the ampoule, hold it in a vertical position, making sure the colored spot (one point cut) is in the same position as shown in the picture.

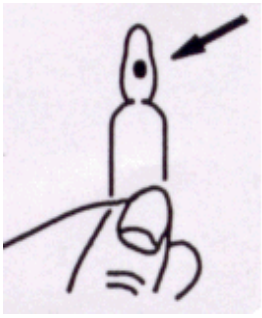


Figure 1

Push the top of the ampoule backwards as shown in the picture.

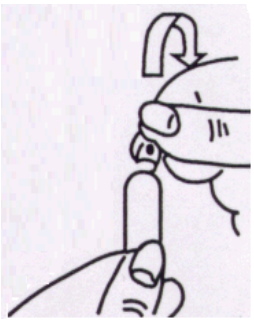


Figure 2

- After adding diluent, shake the vial until the drug has completely dissolved.
- The reconstituted solution is stable for 24 hours at room temperature and for 48 hours in a refrigerator (4ºC-10ºC).

Intravenous administration

- Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose 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.
- 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.

Preparation of the freeze-dried powder for intravenous administration. Dissolve powder in sodium chloride/water for injection. The vial contents are under negative pressure. To minimize aerosol formation during reconstitution; particular care should be taken when the needle is inserted. Inhalation of any aerosol produced during reconstitution must be avoided. Epirubicin should be used within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

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 drug.
- 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(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

9. Details of manufacturer

Manufactured by:
Freeze Dried Powder: M.s. Actavis Italy S.p.A, Viale Pasteur 10, Nerviano-MI-20014, Italy.

Solution for Injection: M/s. Pfizer (Perth) Pty. Ltd, Bentley, 15 Brodie Hall Drive, Western Australia 6102, Australia

Imported and Marketed in India by:

Pfizer Products India Private Limited, The Capital- B Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, India.

10. Details of permission or licence number with date

FF-328-6803 dated 06-May-2020* (*The license is renewed every 3 years as per regulations).
FF-579-19222 dated 04-Jun-2020* (*The license is renewed every 3 years as per regulations).

11. Date of revision

Aug 2021