Epirubicin Hydrochloride Injection I.P.

FARMORUBICIN®

Ready-to-use solution for injection

1. GENERIC NAME

Epirubicin Hydrochloride Injection I.P. Solution for injection (Ready-to-Use)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 2 mg of epirubicin hydrochloride.

List of Excipients

Sodium Chloride,
Hydrochloric Acid,
Water For Injections.

Excipient with known effect

Epirubicin Hydrochloride Injection I.P. Solution for injection 10 mg/5 ml (2 mg/ml) solution for injection contains 17.7 mg of sodium in each vial.

Epirubicin Hydrochloride Injection I.P. Solution for injection 50 mg/25 ml (2 mg/ml) solution for injection contains 88.5 mg of sodium in each vial.

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

3. DOSAGE FORM AND STRENGTH

Solution for injection: 10 mg/5 ml and 50 mg/25 ml (as Ready-to-Use)

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

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
- Sigmoid-Rectal carcinoma
- Soft-tissue sarcomas

4.2 Posology and method of administration

Posology

Epirubicin hydrochloride is a cytotoxic drug that is usually administered to cancer patients by intravenous injection.

Epirubicin hydrochloride is not active when administered orally. It should not be administered intramuscularly or intrathecally.

Intravenous administration

Dosage is typically calculated on the basis of body surface area (mg/m^2). The total epirubicin hydrochloride dose per cycle to be delivered may differ according to its use within a specific treatment regimen (e.g. given as a single agent or in combination with other cytotoxic drugs) and according to the therapeutic indication.

Intravenous administration of epirubicin hydrochloride should be performed with caution. It is advisable to administer the drug via the tubing of a freely-running intravenous saline infusion (0.9% sodium chloride or 5% glucose solution) over 3-20 minutes, depending on the dosage and volume of the infusion solution. This technique is intended to minimise the risk of thrombosis or perivenous extravasation and ensures that the vein will be properly rinsed after administration. Direct intravenous administration is not recommended due to the risk of extravasation, which may occur despite the presence of adequate blood return on aspiration. Tissue damage during extravasation may result in tissue necrosis.

Conventional doses

When epirubicin hydrochloride is used as a single agent, the recommended dose in adults is 60-90 mg/m^2 of body surface area.

The total dose per cycle may be administered in a single dose or divided into multiple doses over 2-3 successive days. A further treatment cycle in the event of normal recovery from drug-induced toxicity (particularly myelosuppression and stomatitis) may be repeated after 3-4 weeks.

High doses

Lung cancer

Epirubicin hydrochloride as a single agent in the high-dose treatment of lung cancer may be administered according to the following regimens:

- small cell lung cancer in previously untreated patients: 120 mg/m^2 on day 1, every 3-4 weeks.
- non-small cell lung cancer (squamous large cell and adenocarcinoma) in previously untreated patients: 135 mg/m^2 on day 1 or 45 mg/m^2 on days 1, 2, 3, every 3 − 4 weeks.

Breast cancer
In the treatment of breast cancer doses of up to 135 mg/m^2 as a single agent and 120 mg/m^2 in combination, every 3-4 weeks, have proven to be effective and well-tolerated.
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100-120 mg/m^{2}every 3-4 weeks are recommended.

Low doses

60-75 mg/m^2 for usual dosage regimens, or 105-120 mg/m^2 for high-dose schedules or a longer interval between cycles is recommended for patients who have been treated or in the presence of neoplastic bone marrow infiltration (see section 4.4 **Special warnings and precautions for use**).

Conventional dose regimens have been used in elderly patients.

If epirubicin hydrochloride is used with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose should be reduced accordingly.

In mild and moderate renal impairment, the dose need not be reduced, because in this way only a limited amount of epirubicin hydrochloride is excreted. Based on the limited availability of data in patients with renal impairment, consideration should be given to lower doses in patients with severe renal impairment (serum creatinine >5 mg/dl, or >442 μmol/l).

Epirubicin hydrochloride is excreted primarily via the hepatobiliary system, dose reduction is therefore necessary in patients with hepatic impairment to avoid increase in general toxicity.

Serum bilirubin	AST	Recommended dose reduction

1.2-3 mg/l	2-4 times the upper limit of normal	50%
>3 mg/l	>4 times the upper limit of normal	75%

4.3 Contraindications

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

- Lactation.

Intravenous use:
- Persistent myelosuppression.
- Severe hepatic impairment.
- Cardiomyopathy.
- 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 a qualified physician experienced in cytotoxic therapy.

The patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) caused by previous cytotoxic therapy before starting 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 effects which are generally similar to the adverse events seen at conventional doses (<90 mg/m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. High dose treatment requires special attention because of the for possibility of clinical complications caused by severe 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 during treatment epirubicin hydrochloride or within 2 to 3 months after treatment termination. Later occurrence (several months after treatment) has also been reported, however. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF), such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm.

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

The risk of developing congestive heart failure increases rapidly with a total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m^2.This cumulative dose may only be exceeded with extreme caution (see section **5.1 Pharmacodynamic properties**, ***Clinical Studies***).

Cardiac function should be evaluated prior to treatment with Epirubicin hydrochloride and should be monitored during treatment in order to minimize the risk of severe cardiac impairment.

The risk may be decreased through regular monitoring of LVEF during treatment with immediate discontinuation of epirubicin hydrochloride at the first signs of impaired cardiac function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) is multi-gated radionuclide angiography (MUGA) or echocardiography. Before commencing treatment, a cardiac evaluation with an ECG and also a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF are required , particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout the monitoring period.

Given the risk of cardiomyopathy, the 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 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 (see section **4.5 Drugs interactions**). The risk of cardiotoxicity during therapy with trastuzumab is also present in patients previously treated with anthracyclinest, although it is lower than in concomitant treatment with trastuzumab and anthracyclines. The increased risk of cardiotoxicity can be also present in patients who receive anthracyclines after treatment with trastuzumab.

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.

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.

There have been sporadic reports of fetal/neonatal cardiotoxic events including fetal death following in utero exposure to epirubicin hydrochloride (see section **4.6 Use in special populations**).

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

Hematologic Toxicity

As with other cytotoxic agents, epirubicin hydrochloride may cause myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin hydrochloride , including differential white blood cell counts. A dose-dependent reversible leukopaenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hydrochloride 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/septicaemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia

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

Gastrointestinal

Epirubicin hydrochloride is emetogenic. Mucositis/stomatitis generally occurs shortly after administration. If severe, it may be progress over several days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Hepatic dysfunction

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 the drug which increases overall toxicity. Lower doses are recommended in these patients (see section **4.2 Posology and method of administration**). Patients with severe hepatic impairment should not be given epirubicin hydrochloride (see section **4.3 Contraindications**).

Renal Function

Serum creatinine should be assessed before and during therapy. The dose of epirubicin hydrochloride should be adjusted in patients with serum creatinine >5 mg/dl or >442 μmol/l (see section **4.2 Posology and method of administration**).

Effects at Site of Injection

Injection into a small vessel or repeated injections into the same vein can cause phlebosclerosis. Following the recommended administration procedures may minimise 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 infusion should be immediately terminated. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g., dexrazoxane (refer to relevant labels for use). The patient's pain may be relieved by cooling down the affected area and keeping it cool, using hyaluronic acid and dimethyl sulphoxide (DMSO). The patient should be monitored closely during the

subsequent period , as necrosis may occur several weeks after extravasation. If 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 hydrochloride.

Tumor-Lysis Syndrome

Epirubicin hydrochloride may induce hyperuricemia as a result of the extensive purine catabolism that accompanies rapid lysis of neoplastic cells (tumor-lysis syndrome) induced by the medicinal product. Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Potential complication of tumour-lysis syndrome may be minimized by hydration, urine alkalinisation, and prophylaxis with allopurinol with the aim of preventing hyperuricemia.

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 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 during treatment and for a period after completion of treatment (see section **4.6 Use in special populations**). Patients planning to have children after completion of therapy are advised to obtain genetic counselling if appropriate and available.

Excipient with known effect:

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

Epirubicin 50mg/25 ml (2 mg /ml) solution for injection contains 88.5 mg of sodium in each vial, equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Drugs interactions

Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs . Additive toxicity may occur especially with regard to bone marrow (haematologic) and the gastro-intestinal tract (see section **4.4 Special warnings and precautions for use**). If epirubicin hydrochloride is used in combination chemotherapy or other potentially

cardiotoxic medicinal products, or if other cardioactive compounds (e.g., calcium channel blockers) are used concomitantly, cardiac function requires monitoring throughout treatment.

Epirubicin hydrochloride is extensively metabolized by the liver. Changes in hepatic function induced by other 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 be at an increased risk of developing cardiotoxicity.

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 metabolites are 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 the administration of these two agents is staggered. The interval between infusion of epirubicin hydrochloride and paclitaxel should be at least 24 hours.

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 penetration of epirubicin hydrochloride into the red blood cells.

The co-administration of interferon alfa-2b 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 haematopoiesis needs to be kept in mind when patients have been previously treated with medications which affects 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

Pregnancy

There is limited amount of data from the use of epirubicin hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section **6.1 Animal Toxicology or Pharmacology**). Epirubicin hydrochloride should not be used during pregnancy only if the potential benefit of treatment outweighs the potential risk to the fetus.

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.

There have been sporadic reports of fetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of fetal death from suspected anthracycline-induced cardiotoxicity following in utero exposure to epirubicin hydrochloride in 2nd and/or 3rd trimesters (see section **4.4 Special warnings and precautions for use**). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.

Breastfeeding

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 and for at least 7 days after last dose.

Fertility

Epirubicin hydrochloride could induce chromosomal damage in human spermatozoa. Epirubicin hydrochloride may cause amenorrhoea or premature menopause in premenopausal women. Based on animal studies, male and female fertility may be irreversibly compromised (see section **6.1 Animal Toxicology or Pharmacology**). It is strongly recommended to seek advice on fertility preservation with men and women prior to treatment.

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

4.7 Effects on ability to drive and use machines

The effect of epirubicin hydrochloride on the ability to drive and use machines has not been systematically evaluated.

4.8 Undesirable effects

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 ≤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 myelosuppression, gastrointestinal reactions, anorexia, alopecia, infection.

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*			Septic shock, Cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Acute myeloid leukaemia, Acute lymphocytic leukaemia			
Blood and lymphatic system disorders	Anaemia, Leukopenia, Neutropenia, Thrombocytopenia Granulocytopenia, Febrile					

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)
	neutropenia					
Immune system disorders				Anaphylactic reaction* Hypersensitivity§		
Metabolism and nutrition disorders		Decreased appetite Dehydration*		Hyperuricaemia*		
Nervous system disorders			Burning sensation	Dizziness		
Eye disorders	Keratitis					
Cardiac disorders		Ventricular tachycardia, Atrioventricular block, Bundle branch block, Bradycardia, Cardiac failure congestive [a]		Cardiotoxicity‖		
Vascular disorders	Hot flush, Phlebitis*	Haemorrhage, * Flushing*	Embolism, Embolism arterial,* Thrombophlebitis*			Shock* Phlebosclerosis
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			Hypoxia[ω]
Gastrointestinal disorders	Nausea, Vomiting,	Oesophagitis,	Gastrointestinal			Abdominal discomfort,

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)
	Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain,* Gastrointestinal erosion,* Gastrointestinal ulcer*	haemorrhage*			Pigmentation buccal, Oral mucosa erosion, Oral pain, Oral discomfort, Mouth haemorrhage
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[†]	Pollakiuria[§]				
Reproductive system and breast disorders	Amenorrhoea			Azoospermia		
General disorders and administration site conditions	Malaise, Pyrexia*	Infusion site erythema Chills*	Asthenia			Soft tissue necrosis[ε], Pain
Investigations	Transaminases abnormal	Ejection fraction decreased				
Injury, poisoning and procedural complications	Chemical cystitis*[§]					Recall phenomenon*[Δ]

[ω] As a result of myelosuppression.
[¶] - including skin rash, itching, fever, chills.
[‖] eg, ECG abnormalities , arrhythmias, cardiomyopathy.
[a] Dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm are mentioned along with this ADR.
[†] Red colouration of urine for 1 to 2 days after administration.

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)
[Δ] Hypersensitivity to irradiated skin (radiation-recall reaction). [ε] After accidental paravenous injection. § Following intravesical administration ADR = adverse drug reaction; ECG = electrocardiogram; EU = European Union; LPD = Local Product Document.						

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 standard treatment procedures.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Epirubicin hydrochloride belongs to the anthracycline cytostatic 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.

At the molecular level, epirubicin hydrochloride 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 can trigger DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin hydrochloride also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin hydrochloride is also involved in

oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin hydrochloride may result from any of the above mechanisms, or other mechanisms.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic, cytotoxic antibiotics and related substances, ATC code: L01DB03

Epirubicin hydrochloride has proved to be effective against a wide spectrum of experimental tumours including leukaemias (LK 1210, P 388), sarcomas (SA 180 solid and ascitic forms), melanoma (B 16), mammary carcinoma , Lewis lung carcinoma and colon carcinoma (38). It has also shown efficacy against human tumours transplanted into athymic mice (melanoma, lung, breast, prostate and ovarian carcinomas).

Clinical Studies

Adjuvant Treatment of Patients with Early Breast Cancer

Two randomized, open-label, multicenter studies evaluated the use of epirubicin hydrochloride 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 **CMF** (total, 6 cycles) N=360	Cyclophosphamide Epirubicin Fluorouracil Cyclophosphamide Methotrexate 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 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
GFEA-05[3] N=565	**FEC-100** (total, 6 cycles) N=276 **FEC-50** (total, 6 cycles) N=289 Tamoxifen 30 mg daily x 3 years, post-menopausal women, any receptor status	Fluorouracil Epirubicin Cyclophosphamide 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 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

[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

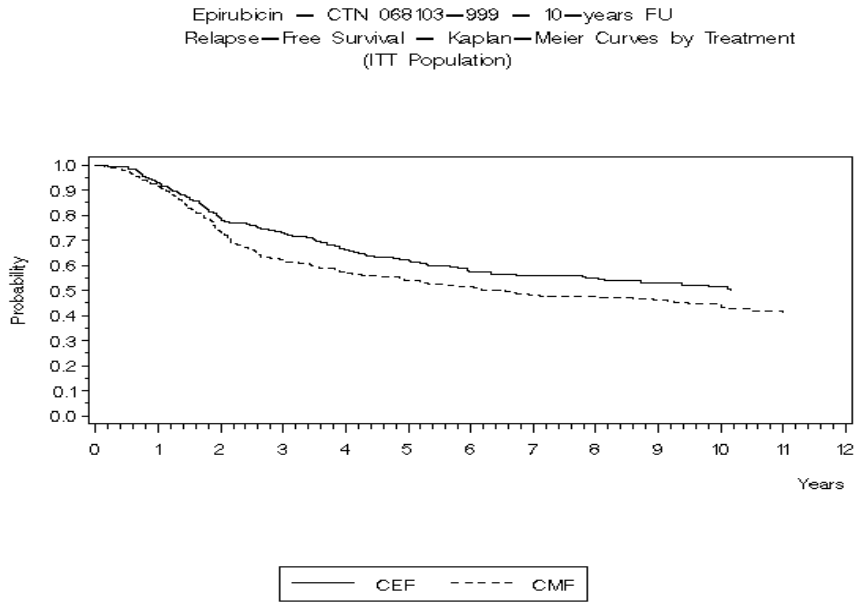


Figure 2. Overall Survival in Study MA-5

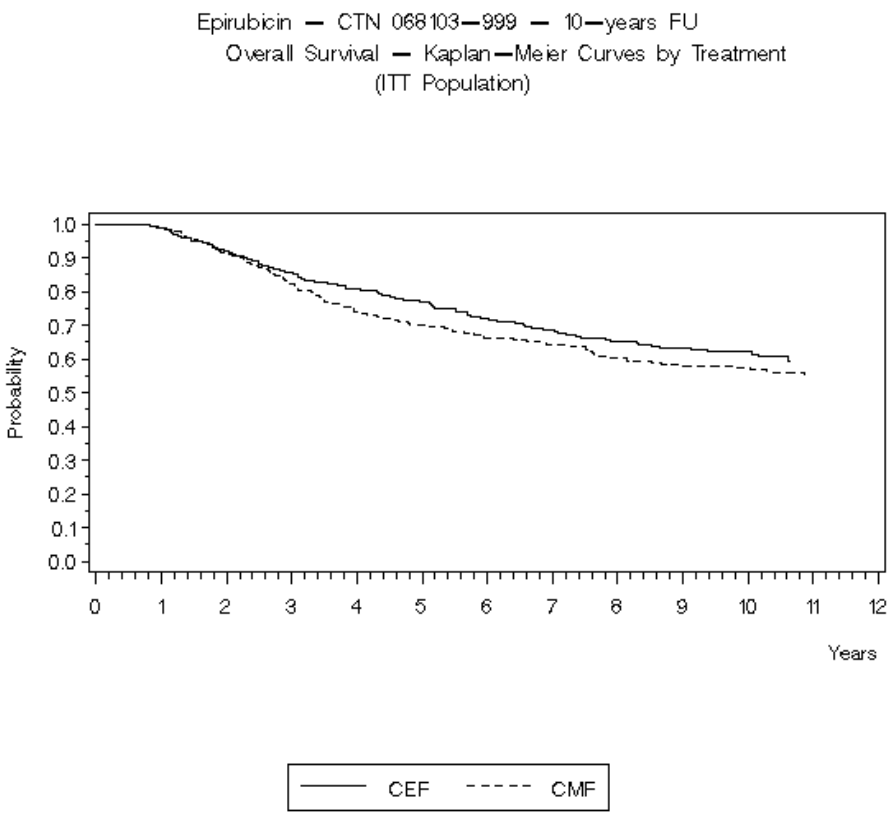


Figure 3. Relapse-free Survival in Study GFEA-05

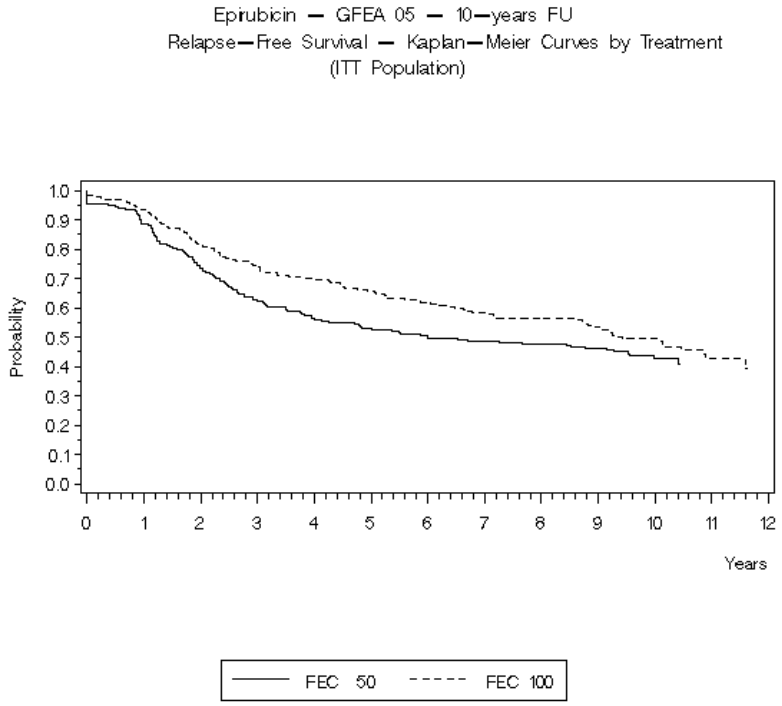
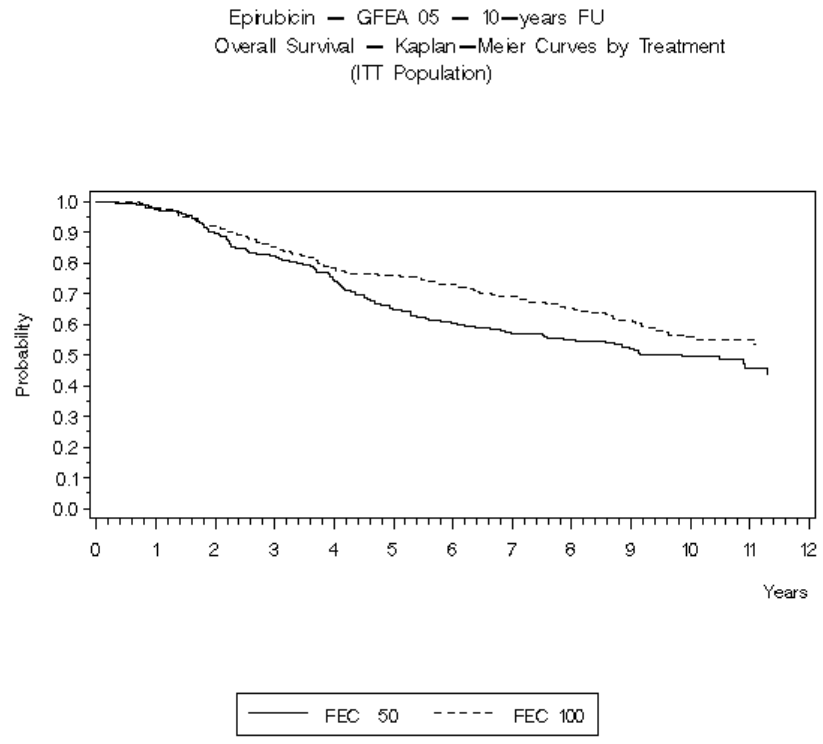


Figure 4. Overall Survival in Study GFEA-05

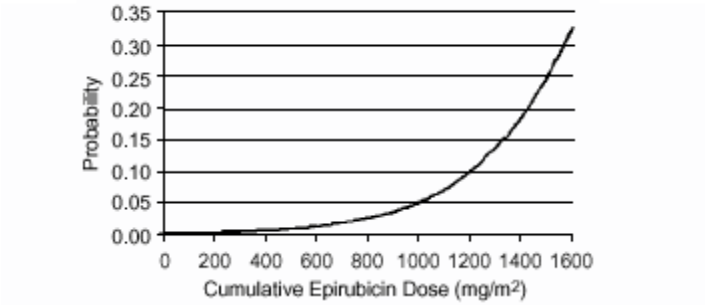


See Table 2 for statistics on 5 and 10 year analyses.

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

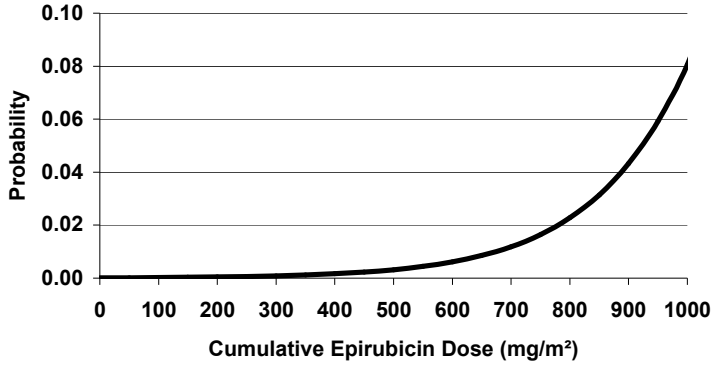


In another retrospective survey of 469 epirubicin-treated patients with metastatic or early breast cancer, the reported risk of CHF was comparable to that observed in the larger study of over 9000 patients.

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 hydrochloride 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

Epirubicin hydrochloride is rapidly and widely distributed into the tissues following intravenous administration. Despite its wide distribution volume epirubicin hydrochloride does not cross the blood-brain barrier in detectable quantities. Binding of epirubicin hydrochloride to plasma proteins, predominantly albumin, is about 77% and is not affected by drug concentration. Epirubicin hydrochloride concentrate in red blood cells; whole blood concentrations are approximately two-fold higher than in plasma.

Biotransformation

Epirubicin hydrochloride is extensively metabolised, particularly by the liver, but also by other organs and cells, including red blood cells. The major metabolites that have been identified are epirubicinol (13-OH epirubicin), which has some degree of antitumour activity (it has *in vitro* cytotoxic activity one-tenth that of epirubicin hydrochloride), and glucuronides of epirubicin and epirubicinol. Plasma levels of epirubicinol are lower than those of the unchanged drug, and they are unlikely to reach *in vivo* concentrations sufficient

for cytotoxicity. No significant activity or toxicity has been reported for the other metabolites.

Elimination

Epirubicin hydrochloride and its major metabolites are mainly excreted via faeces and, to a lesser extent, in the urine. In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of epirubicin hydrochloride follow a tri-exponential fall with a very fast first phase and a slow terminal phase characterised by a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic profile.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Epirubicin hydrochloride is mutagenic, clastogenic and carcinogenic in animals.

The LD_{50} of epirubicin hydrochloride was 29.3 mg/kg in mice, 14.2 mg/kg in rats ,and about 2.0 mg/kg in dogs. Toxicity studies with repeated dosing(in rabbits and dogs), and cardiac toxicity (rats and rabbits) showed that epirubicin hydrochloride is characterized by a lower degree of toxicity than doxorubicin.

The main target organs of toxicity following administration of epirubicin to animals were the hemolymphopoietic system, GI tract, heart, kidney, liver, and reproductive organs.

Epirubicin was toxic to male and female reproductive organs in animal studies. In male rats, administration of epirubicin caused decreases in size/weight of the testes and/or epididymides, and reduced spermatogenesis. In females, epirubicin caused gross alterations in the ovaries and uteri in rats and uterine atrophy in rats and dogs. Epirubicin was embryotoxic and teratogenic when administered during the period of organogenesis in pregnant rats, with an increased incidence of visceral abnormalities observed. However, no malformations were observed in rabbits.

7. DESCRIPTION

Solution for Injection: Clear and clean red solution

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Prolonged contact between epirubicin hydrochloride 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 in certain proportions of drugs can lead to precipitation. Epirubicin hydrochloride can be used in combination with

other anticancer agents, but it is not recommended to mix it with other drugs in the same syringe.

8.2 Shelf-life

36 months

8.3 Packaging information

- 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

Store in a refrigerator at 2°C -8°C in the original package to protect from light until the drug is used.

Store the diluted solution at temperatures not exceeding 25°C for a maximum of 24 hours, at a temperature of 2°C -8°C (in a refrigerator) for a maximum of 48 hours. Any unused solution should be disposed of.

Preparation of the solution

Farmorubicin contains a solution for injection that is ready for administration.

After addition of the solvent, the solution must be mixed until it is completely dissolved. The prepared solution is chemically stable for 24 hours at room temperature and 48 hours in a refrigerator (2°C -8°C). It must be protected from light.

Protective measures

Due to the toxic nature of this substance the following safety recommendations are required:

- Personnel should be trained in the technique of reconstitution and handling.
- Pregnant women should not handle this product.
- Personnel handling with epirubicin hydrochloride should wear protective clothing: goggles, gowns, 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 glass, should be placed in high-risk, waste disposal bags for high temperature incineration.
- In the event of spillage or leakage of the drug, it must be neutralised with dilute sodium hypochlorite (1% available chlorine), then soak up the liquid and use the water.
- All the cleaning materials should be disposed of as described above.

- In case of contact with skin, wash thoroughly with soap and water or sodium bicarbonate. To avoid skin abrasions do not use a scrubbing brush.
- In case of contact with the eyes, hold back the eyelid of the affected eyes and flush with copious amounts of water for at least 15 minutes. Then seek medical advice.
- Always wash your hands after removing gloves.

9. PATIENT COUNSELING INFORMATION

Cardiac Toxicity
Inform patients that there is a risk of irreversible myocardial damage associated with treatment with epirubicin hydrochloride. Advise patients to immediately contact their healthcare provider or to go to an emergency room for new onset of chest pain, shortness of breath, dizziness, or lightheadedness (see section **4.4 Special warnings and precautions for use**).

Secondary Malignancies
Inform patients that there is an increased risk of treatment-related leukemia from epirubicin hydrochloride (see section **4.4 Special warnings and precautions for use**).

Extravasation and Tissue Necrosis
Inform patients that epirubicin hydrochloride can cause severe injection site reactions. Advise patients to contact a healthcare provider if injection site pain occurs after receiving epirubicin hydrochloride (see section **4.4 Special warnings and precautions for use**).

Severe Myelosuppression
Inform patients that epirubicin hydrochloride can cause leukopenia, thrombocytopenia, or anemia. Advise patients to contact a healthcare provider for new onset fever or symptoms of infection (see section **4.4 Special warnings and precautions for use**).

Nausea and Vomiting
Inform patients that epirubicin hydrochloride can cause nausea or vomiting. Advise patients to contact a healthcare provider should they develop any severe symptoms (see section **4.8 Undesirable effects**).

Common Adverse Reactions
Inform patients of the expected adverse effects of epirubicin hydrochloride, including diarrhea, stomatitis, and alopecia (see section **4.8 Undesirable effects**).

Red Coloration of Urine
Advise patients that their urine may appear red for 1 to 2 days after administration of epirubicin hydrochloride and that they should not be alarmed (see section **4.8 Undesirable effects**).

Embryo-Fetal Toxicity
- Advise pregnant women and females of reproductive potential of the potential risk to a fetus, and to inform their healthcare provider of a known or suspected pregnancy

(see section **4.4 Special warnings and precautions for use** and section **4.6 Use in special populations**).

- Advise female patients of reproductive potential to use effective contraception during treatment with epirubicin hydrochloride and for 6 months after the last dose (see section **4.4 Special warnings and precautions for use** and section **4.6 Use in special populations**).
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of epirubicin hydrochloride. Advise male patients with pregnant partners to use condoms during treatment and for at least 7 days after the last dose of epirubicin hydrochloride (see section **4.6 Use in special populations**).

Lactation

Advise female patients not to breastfeed during treatment with epirubicin hydrochloride and for at least 7 days after the last dose (see section **4.6 Use in special populations**).

Infertility

Women treated with epirubicin hydrochloride may develop irreversible amenorrhea, or premature menopause. Advise patients that epirubicin hydrochloride may impair female and male fertility (see section **4.6 Use in special populations**).

10. DETAILS OF MANUFACTURER

Manufactured by:

M/s. Bridgewest Perth Pharma Pty. Ltd, 15 Brodie Hall Drive Bentley, 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.

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

FF-328-6803 dated 19-Mar-2024* (*The license is renewed every 3 years as per regulations).

12. DATE OF REVISION

May 2024