

FARMORUBICIN

(Epirubicin hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

FARMORUBICIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- FARMORUBICIN CS: Sterile Solution for injection containing epirubicin hydrochloride 2 mg per milliliter (mL) in 5 mL and 25 mL solution per vial.
- FARMORUBICIN RD: Freeze dried Powder for solution for injection containing 10 mg and 50 mg, of epirubicin hydrochloride per vial.

3. PHARMACEUTICAL FORM

- Sterile solution for injection.
- Sterile powder for solution for injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

FARMORUBICIN is indicated for the treatment of the following:

- transitional cell bladder cancer^{1-4,124,125,126,127}
- early breast cancer⁵⁻¹¹
- metastatic/advanced breast cancer¹¹⁻²³
- gastro-esophageal cancer²⁴⁻³⁴
- head and neck cancer³⁵⁻³⁷
- primary hepatocellular cancer³⁸⁻⁴⁰
- acute leukemia^{41,42}
- non-small-cell lung cancer⁴³⁻⁴⁸
- small-cell lung cancer⁴⁹⁻⁵³
- non-Hodgkin's lymphoma⁵⁴⁻⁶⁵
- Hodgkin's lymphoma^{66,67}
- multiple myeloma⁶⁸⁻⁷²
- ovarian cancer⁷³⁻⁷⁶
- pancreatic cancer^{77,78}
- hormone-refractory prostatic cancer⁷⁹⁻⁸⁵
- rectal cancer^{86,87}
- soft-tissue and bone sarcomas^{12,88-90}

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

FARMORUBICIN is usually administered by intravenous injection. Intravesical administration has been found beneficial in the treatment of superficial bladder cancer as well as in the prophylaxis of tumor recurrence after transurethral resection. The intra-arterial route of administration has also been used to produce intense local activity with reduced general toxicity (see section 4.4. **Special Warnings and Precautions for Use**).

Intravenous (IV) Administration

The total FARMORUBICIN dose per cycle 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 indication.

FARMORUBICIN should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution). 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.¹¹⁵⁻¹²³ A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see section 4.4. **Special Warnings and Precautions for Use**).

Standard starting dose regimens. As a single agent, the recommended standard starting dose of FARMORUBICIN per cycle in adults is 60-120 mg/m² of body surface area.^{105,128-131} The recommended starting dose of FARMORUBICIN when used as a component of adjuvant therapy in patients with axillary-node positive breast cancer is 100 to 120 mg/m².¹²⁸⁻¹³¹ The total starting dose per cycle may be given as a single dose or divided over 2-3 successive days. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle could be repeated every 3 to 4 weeks. If FARMORUBICIN is used in combination with other cytotoxic drugs with potentially overlapping toxicities the recommended dose per cycle should be reduced accordingly (see reference for specific indication).

High starting dose regimens. High starting doses of FARMORUBICIN may be used in the treatment of breast^{5,12} and lung cancer.^{43,44,47,48,53} As a single agent, the recommended high starting dose of FARMORUBICIN per cycle in adults (up to 135 mg/m²) should be administered on day 1 or in divided doses on days 1, 2, 3, every 3 to 4 weeks. In combination therapy, the recommended high starting dose (up to 120 mg/m²) should be administered on day 1, every 3 to 4 weeks.

Dose Modifications

Renal Dysfunction. While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, lower starting doses should be considered in patients with severe renal impairment (serum creatinine > 5 mg/dL).^{100,102}

Hepatic Dysfunction. Dose reductions are recommended in patients with the following serum chemistry values:^{100,101}

- Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times upper limit of normal:
½ of recommended starting dose.
- Bilirubin > 3 mg/dL or AST > 4 times upper limit of normal:
¼ of recommended starting dose.

Other Special Populations. Lower starting doses or longer intervals between cycles may need to be considered for heavily pre-treated patients or patients with neoplastic bone marrow infiltration (see section 4.4 **Special Warnings and Precautions for Use**). Standard starting doses and regimens have been used in the elderly.¹⁰⁶⁻¹¹⁴

Intravesical Administration

FARMORUBICIN should be instilled using a catheter and retained intravesically for 1 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation. Intravesical administration is not suitable for the treatment of invasive tumors which have penetrated the muscular layer of the bladder wall.¹³⁹

Superficial bladder tumors¹²⁷

Single instillation: A single instillation of 80-100 mg immediately following transurethral resection (TUR) is recommended.^{1,4,124}

4-8 week course followed by monthly instillation: Eight weekly instillations of 50 mg (in 25-50 mL of saline solution) starting 2 to 7 days following TUR are recommended.^{125,126} In the case of local toxicity (chemical cystitis), the dose should be reduced to 30 mg. Patients may receive 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage.^{2,3}

Intra-arterial Administration

Patients with hepatocellular carcinoma may receive a bolus infusion into the main hepatic artery in doses of 60 to 90 mg/m² at intervals of 3 weeks to 3 months or in doses of 40 to 60 mg/m² in 4-week cycles.³⁸⁻⁴⁰

4.3 CONTRAINDICATIONS

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

Intravenous use:

- persistent myelosuppression
- severe hepatic impairment
- cardiomyopathy¹⁴³
- 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**)

Intravesical use:

- urinary tract infections
- inflammation of the bladder
- hematuria¹⁴⁰

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Epirubicin should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy.

Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin hydrochloride (e.g., ≥ 90 mg/m² every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (<90 mg/m² every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin hydrochloride does require special attention for possible clinical complications due to profound myelosuppression.

Cardiac Function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of epirubicin 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 treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin 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/m²; this cumulative dose should only be exceeded with extreme caution (see section **5.1. Pharmacodynamic Properties**).^{91,132}

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 (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO 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/m² 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). 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. Interaction with Other Medicinal Products and Other Forms of Interaction**). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is variable. Trastuzumab 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 anthracyclines are used before this time, careful monitoring of cardiac function is recommended.^{141,144,146}

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.^{91,132}

There have been sporadic reports of fetal/neonatal cardiotoxic events including fetal death following in utero exposure to epirubicin (see Section **4.6. Fertility, Pregnancy and Lactation**).¹⁴⁷

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 pre-leukemic phase, has been reported in patients treated with anthracyclines, including epirubicin.¹³³ Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, 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**).

Gastrointestinal

Epirubicin is emetogenic. 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 is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. 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**). Patients with severe hepatic impairment should not receive epirubicin (see section **4.3. Contraindications**).^{100,101}

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**).^{100,102}

Effects at Site of Injection

Phleboscrosis 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 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, the drug infusion should be immediately stopped.

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.¹⁰³

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 alkalization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.¹⁴²

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route - Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., urethral obstruction due to massive intravesical tumors).

Intra-arterial route - Intra-arterial administration of epirubicin (transcatheter arterial embolization for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Embryo-fetal toxicity

Epirubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with epirubicin (see section **4.6. Fertility, Pregnancy and Lactation**). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Epirubicin is mainly used in combination with other cytotoxic drugs. 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 in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Epirubicin is extensively metabolized by the liver.¹³⁴ Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see section **4.4. Special Warnings and Precautions for Use**).

Cimetidine increased the AUC of epirubicin by 50% and should be stopped during treatment with epirubicin.¹⁰⁴

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites, the latter being, however, neither toxic nor active. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.¹³⁵

4.6 FERTILITY, PREGNANCY AND LACTATION

(see section 5.3. Preclinical Safety Data)

Impairment of Fertility:

Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.^{92-99,147}

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 to use effective contraceptive methods during treatment and for at least 6.5 months after last dose.^{143,147}

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.

Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman. Avoid the use of epirubicin during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of epirubicin during the 2nd and 3rd trimesters.¹⁴⁷

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 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 in 2nd and/or 3rd trimesters (see section 4.4. Special Warning and Precautions for Use). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.^{92-99,147}

Lactation:

It is not known whether epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from epirubicin advise lactating women not to breastfeed during treatment with epirubicin and for at least 7 days after last dose.¹⁴⁷

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8 UNDESIRABLE EFFECTS

A large number of clinical trials with epirubicin, administered at both conventional and high doses in different indications, have been conducted. Serious drug-related adverse events that occurred during clinical trials are listed below. Data from post-marketing surveillance are also included.

Table 1: Adverse Drug Reaction Table¹⁴⁵

System Organ Class	Adverse Drug Reactions
Infections and infestations	Sepsis*
	Pneumonia*
	Conjunctivitis
	Infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Acute myeloid leukaemia
	Acute lymphocytic leukaemia
Blood and lymphatic system disorders	Febrile neutropenia
	Leukopenia
	Neutropenia
	Thrombocytopenia
	Anaemia
Immune system disorders	Anaphylactic reaction*
Metabolism and nutrition disorders	Dehydration*
	Hyperuricaemia*
	Decreased appetite
Eye disorders	Keratitis
Cardiac disorders	Cardiac failure congestive
	Ventricular tachycardia
	Atrioventricular block
	Bundle branch block
	Bradycardia
Vascular disorders	Shock*
	Haemorrhage*
	Embolism arterial*
	Embolism
	Thrombophlebitis*
	Phlebitis*
	Hot flush
	Flushing*
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism*
Gastrointestinal disorders	Gastrointestinal haemorrhage*
	Gastrointestinal ulcer*
	Diarrhoea
	Mucosal inflammation
	Stomatitis
	Vomiting
	Gastrointestinal erosion*
	Gastrointestinal pain*
	Abdominal discomfort
	Nausea
	Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia
	Skin toxicity
	Photosensitivity reaction*
	Rash/Pruritus
	Skin disorder
	Erythema*
	Skin hyperpigmentation*
Nail pigmentation*	

	Urticaria*
Renal and urinary disorders	Chromaturia*†
Reproductive system and breast disorders	Amenorrhoea
General disorders and administration site conditions	Asthenia
	Chills*
	Pyrexia*
	Malaise
Investigations	Ejection fraction decreased
	Transaminases abnormal
Injury, poisoning and procedural complications	Chemical cystitis*§
	Recall phenomenon*Δ

* ADR identified post-marketing.

† Red coloration of urine for 1 to 2 days after administration.

§ Following intravesical administration.

Δ Hypersensitivity to irradiated skin (radiation-recall reaction).

4.9. OVERDOSE

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES^{136,137}

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 cytotoxic 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.

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/m² 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).^{21,22,128-131} Study MA-5^{22,128,129} evaluated 120 mg/m² of epirubicin hydrochloride 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

hydrochloride -containing CEF-120 regimen or to a CMF regimen. Study GFEA-05^{21,130,131} evaluated the use of 100 mg/m² of epirubicin hydrochloride 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 2 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 2 Treatment Regimens Used in Phase 3 Studies of Patients with Early Breast Cancer^{21,22,128-131}

	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 hydrochloride 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 days
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 hydrochloride Cyclophosphamide Fluorouracil Epirubicin hydrochloride 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.^{22,128,129} In the GFEA-05 study, the median age was 51 years and approximately half of the patients were post-menopausal.^{21,130,131} 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 3. Results after up to 10 years of follow-up are presented in Table 3. In Study MA-5, epirubicin hydrochloride -containing combination therapy (CEF-120) showed significantly longer RFS than CMF (5-year estimates were 62% versus 53%, stratified logrank 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 hydrochloride -containing CEF-120 regimen than for the CMF regimen (5-year estimate 77% versus 70%; stratified logrank for overall survival $p = 0.043$; non-stratified logrank $p = 0.13$). The estimated reduction in the risk of death was 29% at 5 years.^{22,128,129}

In Study GFEA-05, patients treated with the higher-dose epirubicin hydrochloride regimen (FEC-100) had a significantly longer 5-year RFS (estimated 65% versus 52%, logrank for the overall RFS $p = 0.007$) and OS (estimated 76% versus 65%, logrank 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.^{21,130,131}

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 3.^{21,22,128-131}

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.^{22,128,129} 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.^{21,130,131}

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

	MA-5 Study ^{22,128,129}		GFEA-05 Study ^{21, 130,131}	
	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^{22,128,129} are shown in Figures 1 and 2 and those for Study GFEA-05^{21,130,131} are shown in Figures 3 and 4.

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

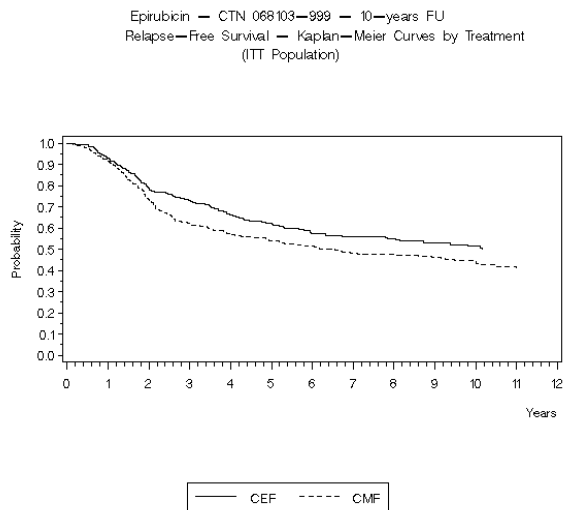


Figure 2. Overall Survival in Study MA-5

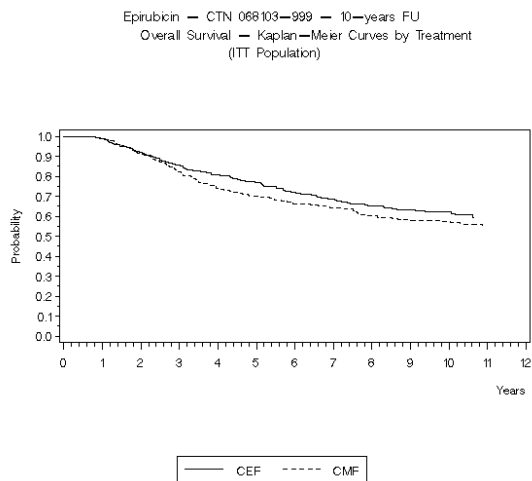
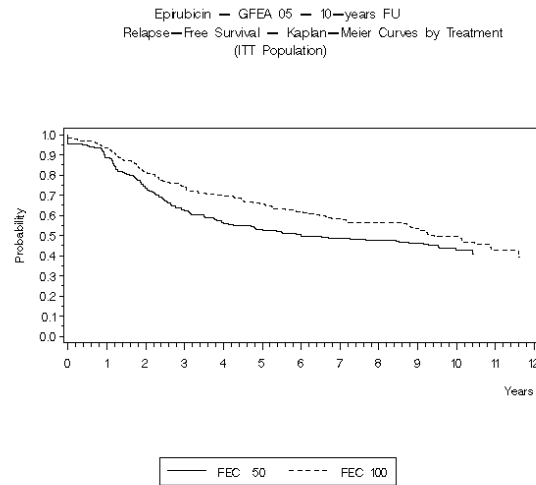
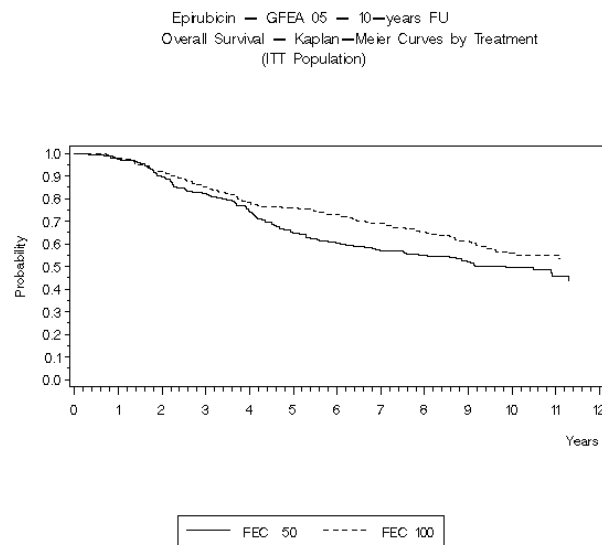
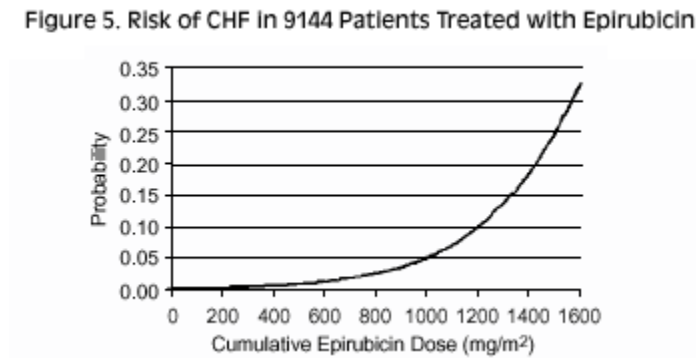


Figure 3. Relapse-Free Survival in Study GFEA-05**Figure 4. Overall Survival in Study GFEA-05**

See Table 3 for statistics on 5 and 10 year analyses.

Cardiac Function

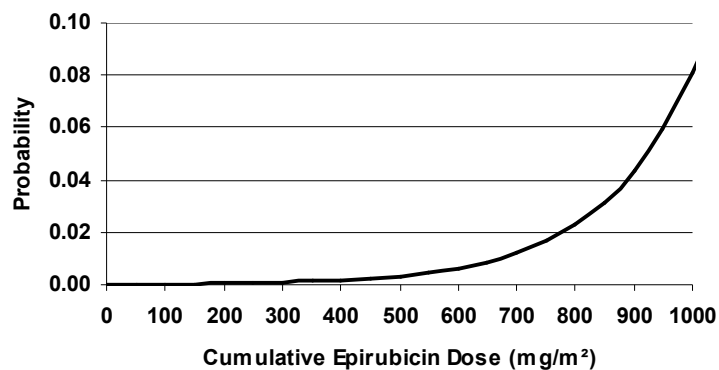
In a retrospective survey, including 9144 patients, mostly with solid tumors in advanced stages, the probability of developing CHF increased with increasing cumulative doses of epirubicin hydrochloride (Figure 5). The estimated risk of epirubicin hydrochloride -treated patients developing clinically evident CHF was 0.9% at a cumulative dose of 550 mg/m², 1.6% at 700 mg/m², and 3.3% at 900 mg/m². In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m². The risk of developing CHF in the absence of other cardiac risk factors increased steeply after an epirubicin hydrochloride cumulative dose of 900 mg/m².⁹¹

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

In another retrospective survey of 469 epirubicin hydrochloride -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.¹³²

Secondary Leukemia

An analysis of 7110 patients who received adjuvant treatment with epirubicin hydrochloride 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 years¹³³. The risk of developing AML/MDS increased with increasing epirubicin hydrochloride cumulative doses as shown in Figure 6.

Figure 6. Risk of AML/MDS in 7110 Patients Treated with Epirubicin hydrochloride¹³³

AML/MDS rates increased with epirubicin hydrochloride dose per cycle, and cumulative dose. For instance, in the MA-5 trial, in patients that received intensive doses of epirubicin hydrochloride (120 mg/m²), 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.¹³³

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 hydrochloride (720 mg/m²) or cyclophosphamide (6,300 mg/m²), as shown in Table 4.¹³³

Table 4. Cumulative probability of AML/MDS in relation to cumulative doses of epirubicin hydrochloride and cyclophosphamide

Years from Treatment Start	Cumulative Probability of Developing AML/MDS % (95% CI)							
	Cyclophosphamide ≤6,300 mg/m ²				Cyclophosphamide >6,300 mg/m ²			
	Epirubicin hydrochloride Cumulative Dose ≤720 mg/m ² N=4760		Epirubicin hydrochloride Cumulative Dose >720 mg/m ² N=111		Epirubicin hydrochloride Cumulative Dose ≤720 mg/m ² N=890		Epirubicin hydrochloride 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)	

5.2. PHARMACOKINETIC PROPERTIES^{136,137}

Epirubicin hydrochloride pharmacokinetics are linear over the dose range of 60 to 150 mg/m² 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*¹³⁴

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 hydrochloride doses of 12.5 to 90 mg/m². 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 hydrochloride dose of 25 mg/m² (n = 8). Their pharmacokinetics were compared to those of patients with normal serum AST and bilirubin values, who received epirubicin hydrochloride doses of 12.5 to 120 mg/m². The median plasma clearance of epirubicin hydrochloride 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.^{100,101} (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 hydrochloride 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^{100,102} (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.

5.3. PRECLINICAL SAFETY DATA

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals.^{92-99,136,137}

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

- Powder vial: Lactose monohydrate
- Solution: Sodium Chloride, Hydrochloric Acid & Water For Injection

6.2. INCOMPATIBILITIES

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

6.3. SHELF LIFE

- FARMORUBICIN RD powder for injection: 36 months
- FARMORUBICIN CS sterile solution for injection: 24 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

- FARMORUBICIN RD powder for injection: Store at controlled temperature 15-30°C.
- FARMORUBICIN CS sterile solution for injection: Store at 2-8°C

Ready-to-use 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 (15 – 25°C).¹³⁸

6.5. NATURE AND CONTENTS OF CONTAINER

- Powder: Type III glass vial
- Solution: Polypropylene vial with Teflon faced rubber stopper

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of the freeze-dried powder for intravenous administration

Dissolve in sodium chloride/water for injection. The vial contents will be under a 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.

FARMORUBICIN 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, disposable gloves and masks;
- A designated area should be defined for reconstitution (preferably under a laminar flow system); the work surface should be protected by disposable, plastic-backed, absorbent paper;
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration;
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water;
- All cleaning materials should be disposed of as indicated previously;
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.
- In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.

- Always wash hands after removing gloves.

Farmorubicin/LPD/PK-04

According to CDS V 10 dated: 08 January 2021; Supersedes CDS V 09 dated: 21 November 2018

Imported & Marketed by:
Pfizer Pakistan Limited

Please visit our website www.pfizerpro.com.pk for latest version of Product leaflet.

7. REFERENCES

1. Rajala P, *et al.* Transurethral resection with perioperative instillation on interferon-alpha or epirubicin for the prophylaxis of recurrent primary superficial bladder cancer: a prospective randomized multicenter study-Finnbladder III. *J Urol* 161(4), 1133-1135, 1999.
2. Melekos MD, *et al.* Intravesical bacillus Calmette-Guerin versus epirubicin in the prophylaxis of recurrent and/or multiple superficial bladder tumours. *Oncology* 53(4):281-288, 1996.
3. Raitanen MP, Lukkarinen O. A controlled study of intravesical epirubicin with or without alpha 2b-interferon as prophylaxis for recurrent superficial transitional cell carcinoma of the bladder. Finnish multicentre study group. *Br J Urol* 76(6):697-701, 1995.
4. Oosterlinck W, *et al.* A prospective European organization for research and treatment of cancer genitourinary group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage TA, T1 papillary carcinoma of the bladder. *J Urol* 149(4):749-752, 1993.
5. Wils J. *et al.* Multicenter, international, randomised phase III study comparing epirubicin plus tamoxifen with alone in postmenopausal women with node positive early breast cancer (Document 9650308). *Wils JA Epirubicin plus tamoxifen versus tamoxifen alone in node-positive postmenopausal patients with breast cancer: a randomized trial of the international collaborative cancer group. J Clin Oncol* 17(7):1988-1998, 1999.
6. Deleted in CDS revision dated October 18, 2005.
7. Di Leo, *et al.* CMF or anthracycline-based adjuvant chemotherapy for node-positive (N+) breast cancer (BC) patients (PTS): 4 year results of a Belgian randomised clinical trial with predictive markers analysis. *Pros ASCO*. Vol 18,0 No. 258, 1999.
8. Fumoleau P, *et al.* Better outcome of premenopausal node-positive (N+) breast cancer patients (pts) treated with 6 cycles vs 3 cycles of adjuvant chemotherapy: eight year follow-up results of FASG 01. *Proc ASCO*, Vol 18, No. 252, 1999.
9. Mouridsen HT, *et al.* Adjuvant anthracycline in breast cancer. Improved outcome in premenopausal patients following substitution of methotrexate in the CMF combination with epirubicin. *Proc ASCO*, Vol 18. No. 254, 1999.
10. Bonnetterre J, *et al.* Results of a randomized trial of adjuvant chemotherapy with FEC50 vs FEC 100 in high risk node-positive breast cancer patients. *Proc ASCO* Vol 17, No. 473, 1998.
11. Coombes RC, *et al.* Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The international collaborative cancer group. *J Clin Oncol* 14(1):35-45, 1996.
12. Lopez M, *et al.* Randomized prospective clinical trial of high-dose epirubicin and dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas. *J Clin Oncol* 16(1):86-92, 1998.

13. Blackstein M. *et al.* Epirubicin high dose versus conventional dose in metastatic breast cancer: A randomised study in women after CMF failure (Document 9650082)
14. Focan C. *et al.* Dose response relationship of an epirubicin based first line chemotherapy for advanced breast cancer. A prospective randomised phase III trial. (Document 9650083) *Focan C. et al. Dose response relationship of an epirubicin based first line chemotherapy for advanced breast cancer. A prospective randomised phase III trial. J Clin Oncol 11(7):253-1263, 1993.*
15. French Epirubicin Study Group. A prospective randomized phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil, and either doxorubicin or epirubicin. *J Clin Oncol 6(4):679-688, 1988.*
16. Italian Multicentre Breast Study with Epirubicin. Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide v fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial. *J Clin Oncol 6(6):976-982, 1988.*
17. Perez DJ, *et al.* A randomized comparison of single-agent doxorubicin and epirubicin as first-line cytotoxic therapy in advanced breast cancer. *J Clin Oncol 9(12):2148-2152, 1991.*
18. Habeshaw T, *et al.* Epirubicin at two dose levels with prednisolone as treatment for advanced breast cancer: the results of a randomized trial. *J Clin Oncol 9(2):295-304, 1991.*
19. Jain KK, *et al.* A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol 3(6):818-826, 1985.*
20. Bastholt L, *et al.* Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish breast cancer cooperative group. *J Clin Oncol 14(4):1146-1155, 1996.*
21. Colajori E. *et al.* Multicenter, International, Randomised Phase III Study Comparing High Dose to Conventional Dose Epirubicin in Combination with Cyclophosphamide and 5-Fluorouracil as Primary Therapy in Advanced Breast Cancer Patients (Document 9550091) (Addendum Document 9850333).
22. Colajori E, *et al.*: Multinational, randomised, phase III, open study comparing an intensive Epirubicin containing regimen including Cyclophosphamide and 5-Fluorouracil with a conventional non-anthracycline combination in patients with metastatic Breast Cancer (Document 9550092) (Addendum Document 9850334) *Colajori E, et al. IV FEC with epirubicin (E) 50 mg/m² D1,8 prolongs time to progression (TTP) with respect to IV CMF D1,8 given at equimyelosuppressive doses as front line chemotherapy of metastatic breast cancer (MBC): a randomized multinational multicentric phase III trial. Proc ASCO. Vol 14, No. 156, 1995.*
23. Brufman G, *et al.* Doubling epirubicin dose intensity (100 mg/m² versus 50 mg/m²) in the FEC regimen significantly increases response rates. An international randomised phase III study in metastatic breast cancer. *Ann Oncol 8:155-162, 1997.*
24. Waters JS. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer 80(1-2):269-272, 1999.*

25. Chi KH, *et al.* Weekly etoposide, epirubicin, cisplatin, 5-fluorouracil and leucovorin: an effective chemotherapy in advanced gastric cancer. *Br J Cancer* 77(11):1984-1988, 1998.
26. Bouillot JL, *et al.* Adjuvant chemotherapy using fluoro-uracil, epirubicin and cisplatin (FEP) after curative resection of gastric carcinoma. *Br J Surg* 85(suppl 2) 1998 [Abs].
27. Zaniboni A, *et al.* Epirubicin, cisplatin, and continuous infusion 5-fluorouracil is an active and safe regimen for patients with advanced gastric cancer. *Cancer* 76:1694-6199, 1995.
28. Webb A, *et al.* Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 15(1):261-267, 1997.
29. Bamias A, *et al.* Epirubicin, cisplatin, and protracted venous infusion of 5-fluorouracil for esophagogastric adenocarcinoma. *Cancer* 77:1978-1985, 1996.
30. Melcher AA, *et al.* Epirubicin, cisplatin and continuous infusion 5-fluorouracil (ECF) as neoadjuvant chemotherapy in gastro-oesophageal cancer. *Br J Cancer* 74(10): 1651-1654, 1996.
31. Bamias A, *et al.* Adjuvant chemotherapy for oesophagogastric cancer with epirubicin. *Br J Cancer* 71:583-586, 1995.
32. Roelofs EJM, *et al.* Phase II study of sequential high-dose methotrexate (MTX) and 5-fluorouracil (F) alternated with epirubicin (E) and cisplatin (P) [FEMTX-P] in advanced gastric cancer. *Ann Oncol* 4:426-428, 1993.
33. Cervantes A, *et al.* 5-fluorouracil, folinic acid, epidoxorubicin and cisplatin (FLEP) combination chemotherapy in advanced measurable gastric cancer. A phase II trial of the Spanish cooperative groups for gastrointestinal tumor therapy (TTD). *Ann Oncol* 4:753-757, 1993.
34. Cocconi G. *et al.*: A prospective randomized trial comparing FAM combination with PELF combination in advanced gastric carcinoma. *Proc ASCO Vol.11; No. 468. p163*, 1992.
35. International Nasopharynx Cancer Study Group. VUMCA I trial. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. *Int J Radiat Oncol Biol Phys* 35(3):463-469, 1996.
36. Maipang T, *et al.* Cisplatin-epirubicin chemotherapy for advanced unresectable squamous cell carcinoma of the head and neck. *Head Neck* 15(2):109-114, 1993.
37. Guaraldi M. *et al.*: Treatment of advanced head and neck tumors with PEV-B regimen: a pilot study. *Chemioterapia* 7; 341-344, 1988.
38. Epirubicin Study Group for Hepatocellular Carcinoma. Intra-arterial administration of epirubicin in the treatment of nonresectable hepatocellular carcinoma. *Cancer Chemother Pharmacol* 19; 183-189, 1987.

39. Kajanti m. *et al*: Intra-arterial and intravenous use of 4'-epidoxorubicin combined with 5-fluorouracil in primary hepatocellular carcinoma. *Am J Clin Oncol* 15; 37-40, 1992.
40. Ellis PA, *et al*. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. *Eur J Cancer* 31A(10):1594-1598, 1995.
41. Liso V, *et al*. Continuous infusion chemotherapy with epirubicin and vincristine in relapsed and refractory acute leukemia. *Acta Haematol* 83:116-119, 1990.
42. Sampi,K, *et al*. A phase II study of epirubicin in acute leukemia: a cooperative group study. *Anticancer Res* 7:29-32, 1987.
43. Fetscher S, *et al*. Dose-intense therapy with etoposide, ifosfamide, cisplatin, and epirubicin (VIP-E) in 107 consecutive patients with limited- and extensive-stage non-small-cell lung cancer. *Ann Oncol* 8:57-64, 1997.
44. Martoni A, *et al*. Phase III trial on high-dose epirubicin (H.D. Epi) + cisplatinum (CP) vs. vinorelbine (VNR) + CP in advanced non small cell lung cancer (NSCLC). *Proc ASCO Vol* 15. No. 1108, 1996.
45. Comella P, *et al*. Alternated approach with local irradiation and combination chemotherapy including cisplatin or carboplatin plus epirubicin and etoposide in intermediate stage non-small-cell lung cancer. *Cancer* 74:1874-1881, 1994.
46. Feld R, *et al*. Phase I-II study of high-dose epirubicin in advanced non-small-cell lung cancer. *J Clin Oncol* 10(2):297-303, 1992.
47. Martoni A. *et al*: A phase II study of high-dose epirubicin plus cisplatinum in advanced non-small-cell lung cancer (NSCLC). *Annals of Oncology* 3; 864–866, 1992.
48. Smit EF, *et al*. A phase II study of high dose epirubicin in unresectable non small cell lung cancer. *Br J Cancer* 65(3):405-408, 1992.
49. Gómez-Codina J, *et al*. Randomized trial of high-dose epirubicin-cisplatin versus etoposide-cisplatin in small-cell lung cancer. *Proc ASCO Vol* 18. No. 1810, 1999.
50. Fetscher S, *et al*. Dose-intense therapy with etoposide, ifosfamide, cisplatin, and epirubicin (VIP-E) in 100 consecutive patients with limited- and extensive-disease small-cell lung cancer. *Ann Oncol* 8:49-56, 1997.
51. Jassem J, *et al*. Combination chemotherapy with vincristine, epirubicin and cyclophosphamide in small cell lung carcinoma. *Eur J Cancer* 28(2/3):473-476, 1992.
52. Quoix EA, *et al*. Epirubicin in previously untreated patients with small cell lung cancer: a phase II study by the EORTC lung cancer cooperative group. *Eur J Cancer* 28A(10):1667-1670, 1992.
53. Blackstein M. Epirubicin in extensive small-cell lung cancer: a phase II study in previously untreated patients: a national cancer institute of Canada clinical trials group study. *J Clin Oncol* 8(3):385-389, 1990.

54. Chim CS, *et al.* CEOP treatment results and validity of the international prognostic index in Chinese patients with aggressive non-Hodgkin's lymphoma. *Hematol Oncol* 16:117-123, 1998.
55. Nair R, *et al.* A randomized comparison of the efficacy and toxicity of epirubicin and doxorubicin in the treatment of patients with non-Hodgkin's lymphoma. *Cancer* 82:2282-2288, 1998.
56. Fridrik MA, *et al.* CEOP-IMVP-DEXA in the treatment of aggressive lymphomas: an austrian multicenter trial. *J Clin Oncol* 14(1):227-232, 1996.
57. DeLena M, *et al.* CEOP-B alternated with VIMB in intermediate-grade and high-grade non-Hodgkin's lymphoma: a pilot study. *J Clin Oncol* 13(4):953-96, 1995.
58. Deliliers GL, *et al.* A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. *Haematologica* 80:318-324, 1995.
59. Zinzani P.L. *et al.*: CEOP regimen in the treatment of advanced low-grade non-Hodgkin's lymphomas: preliminary report. *Tumori* 76; 533-636, 1990.
60. DeLena M, *et al.* Comparison of CHOP-B vs CEOP_B in 'poor prognosis' non-Hodgkin's lymphomas. A randomized trial. *Med Oncol & Tumor Pharmacother.* 6(2):163-169, 1989.
61. Al-Ismail SAD, *et al.* Combination chemotherapy including epirubicin for the management of non-Hodgkin's lymphoma. *Eur J Cancer Clin Oncol.* 23(9):1379-1384, 1987.
62. Zuckerman KS, Case CDJ, Gams RA, Prasthofer EF. Chemotherapy of intermediate- and high-grade non-Hodgkin's lymphomas with an intensive epirubicin-containing regimen. *Blood.*1993;82:3564-3573.
63. McQuaker IG, Haynes, AP, Stainer C, *et al.* Stem Cell mobilation in resistant or relapsed lymphoma; superior yield of progenitor cells following a salvage regimen comprising ifosphamide, etoposide, and epirubicin, compared to intermediate-dose cyclophosphamide. *Br J Haematol.*98:228-233, 1997.
64. O'Reilly SE, Connors JM, Howdle S, *et al.* In search of an optimal regimen for elderly patients with advanced-stage diffuse large-cell lymphoma; results of a phase II study of P/DOCE chemotherapy. *J Clin Oncol* 11:2250-2257, 1993.
65. Hill M, Milan S, Cunningham D, *et al.* Evaluation of the efficacy of the VEEP regimen in adult Hodgkin's disease with assessment of gonadal and cardiac toxicity [see comments]. *J Clin Oncol.*13:387-395, 1995.
66. Avilés A, *et al.* Results of a randomized study of early stage Hodgkin's disease using ABVD, EBVD, or MBVD. *Med Pediatr Oncol* 24:171-175, 1995.
67. Gobbi PG, *et al.* MOOP/EBV/CAD hybrid chemotherapy with or without limited radiotherapy in advanced or unfavorably presenting Hodgkin's disease: a report from the Italian lymphoma study group. *J Clin Oncol* 11(4):712-719, 1993.
68. Fossa A, *et al.* Bolus vincristine and epirubicin with cyclophosphamide and dexamethasone (VECD) as induction and salvage treatment in multiple myeloma. *Leukemia* 12:422-426, 1998.

69. Vincent M, Goss G, Sinoff C, *et al.* Bi-weekly vincristine, epirubicin, and methylprednisolone in alkylator-refractory multiple myeloma. *Cancer Chemother Pharmacol* 34:356–360, 1994.
70. Aviles A, Delgado S, Nambo MJ, *et al.* Adjuvant radiotherapy to sites of previous bulky disease in patients with stage IV diffuse large-cell lymphoma. In *J Radiat Oncol Biol Phys* 30:799–803, 1994.
71. Case DC, *et al* Phase I-II study of epirubicin in multiple myeloma. *Cancer Res* 48:6246-6248, 1988.
72. Brugnatelli S, Riccardi A, Ucci G, *et al.* Experience with poorly myelosuppressive chemotherapy schedules for advanced myeloma. The Cooperative Group of Study and Treatment of Multiple Myeloma. *Br J Cancer*.73:794–797, 1996.
73. Wils J, *et al.* Cyclophosphamide, epirubicin and cisplatin (CEP versus epirubicin plus cisplatin (EP) in stage Ic-IV ovarian cancer: a randomized phase III trial of the gynecologic oncology group of the comprehensive cancer center Limburg. *Anti-Cancer Drugs* 10:257-261, 1999.
74. Conte PF, *et al.* High-dose versus low-dose cisplatin in combination with cyclophosphamide and epidoxorubicin in suboptimal ovarian cancer: a randomized study of the gruppo oncologico Nord-Ovest. *J Clin Oncol* 14(2):351-356, 1996.
75. Peláez, *et al.* Phase II trial of epirubicin at standard dose in relapsed ovarian cancer. *Eur J Cancer* 32A(5):899-900, 1996.
76. Pronzato P, *et al.* A feasibility study of accelerated polychemotherapy with cisplatin, epidoxorubicin and cyclophosphamide (PEC) in advanced ovarian cancer. *Br J Ca* 73:1425-1427, 1996.
77. Topham C. *et al*: Randomised trial of epirubicin alone versus 5-fluorouracil, epirubicin and mitomycin C in locally advanced and metastatic carcinoma of the pancreas. *Br J Cancer* 64;179-181, 1991.
78. Wagener DJ.TH, *et al.* Results of a phase II trial of epirubicin and cisplatin (EP) before and after irradiation and 5-fluorouracil in locally advanced pancreatic cancer: an EORTC GITCCG study. *Eur J Cancer* 32A(8):1310-1313, 1996.
79. Di Leo A, Bajetta E, Buzzoni R, *et al.* Epirubicin plus medroxyprogesterone as second-line treatment of advanced prostatic cancer. *Am J Clin Oncol* 18(3):239-244, 1995.
80. Fuse H, Muraishi Y, Fujishiro Y, Katayama. Etoposide, epirubicin and carboplatin in hormone-refractory prostate cancer. *Int Urol Nephrol* 28(1):79-85, 1996.
81. Brausi M, Jones WG, Fosså SD, *et al.* High dose epirubicin is effective in measurable metastatic prostate cancer: a phase II study of the EORTC genitourinary group. *Eur J Cancer* 31A(10):1622-1626, 1995.
82. Anderström C, *et al.* Epirubicin and medroxyprogesterone acetate versus estramustine phosphate in hormone-resistant prostatic cancer: a prospective randomized study. *Eur Urol* 27:301-305, 1995.

83. Delaere KP, *et al.* Phase II study of epirubicin in advanced hormone-resistant prostatic carcinoma. *Br J Urol* 70:641-642, 1992.
84. Pummer K. Epirubicin plus flutamide and orchidectomy in previously untreated advanced prostatic cancer. *Semin Oncol* 18(5):26-28, 1991.
85. Francini G, Petrioli R, Manganelli A, *et al.* Weekly chemotherapy in advanced prostatic cancer. *Br J Cancer* 67:1430-1436, 1993.
86. Pyrhonen SO, Kouri MO. Phase II study of epirubicin sequential methotrexate and 5-fluorouracil for advanced colorectal cancer. *Eur J. Cancer* 28A (11):1828-1832, 1992.
87. Raderer *et al.* Tolerance of the novel chemo-sensitizer dexverapamil in combination with anthracycline chemotherapy: a prospective toxicity analysis in advanced gastrointestinal cancer. *Onkologie* 18(5):462-467, 1995.
88. Jelic S, *et al* Randomised study of high-dose epirubicin versus high-dose epirubicin-cisplatin chemotherapy for advanced soft tissue sarcoma. *Eur J Cancer* 33:220-225, 1997.
89. Palumbo R, *et al.* Dose-intensive first-line chemotherapy with epirubicin and continuous infusion ifosfamide in adult patients with advanced soft tissue sarcomas: a phase II study. *Eur J Cancer* 35(1):66-72, 1999.
90. Mouridsen H.T. *et al:* Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC soft tissue and bone sarcoma group. *Eur J Cancer and Clin Oncol* 23; 1477–1483, 1987.
91. Praga C, *et al.* Anthracycline-induced cardiotoxicity and its relevance in cancer treatment. In Nimmo WS & AL: *Clinical Measurement in Drug Evaluation*. Wolfe, Publishing Ltd, London, 1991, 131-142.
92. Castellino S. Microbiological study of mutagenesis with epirubicin in comparison with doxorubicin. Gene mutation test *in vitro* on *Salmonella typhimurium* according to Ames. Farmitalia Carlo Erba Technical Report IMI 28/313i, June 1983.
93. Castellino S. Cytological study of mutagenesis with epirubicin in comparison with epirubicin. *In vitro* gene mutation test on the V79 Chinese hamster cell line. Farmitalia Carlo Erba Technical Report IMI 28/312i, June 1983.
94. Trane F. Cytogenetic test of mutagenesis with epirubicin HCl in comparison with doxorubicin HCl. Induction of chromosome aberrations in human lymphocytes grown *in vitro*. Farmitalia Carlo Erba Technical Report IMI 28/318i, October 1984.
95. Trane F. Cytogenetic test of mutagenesis with epirubicin HCl in comparison with doxorubicin HCl. Induction of chromosome aberrations in mouse bone marrow cells after intravenous administration. Farmitalia Carlo Erba Technical Report IMI 28/317i, October 1984.
96. Mazué G, Williams GM, Iatropoulos MJ, *et al.* Anthracyclines: review of genotoxicity and carcinogenicity studies. *Int J Oncol* 8:525-536, 1996.

97. Beltrame D. PNU-159378 (epirubicin): explorative embryotoxicity study in the rat by intravenous route. Pharmacia & Upjohn Final Abbreviated Report 9850197, July 1998.
98. Beltrame D. PNU-159378 (epirubicin): explorative embryotoxicity study in the rabbit by intravenous route. Pharmacia & Upjohn Final Abbreviated Report 9850197, July 1998.
99. Shimazu H. Preliminary study by intravenous administration of epirubicin hydrochloride (IMI-28) during the perinatal and lactation periods in rats. Farmitalia Carlo Erba Technical Report IMI 28/434i; January 1985.
100. Camaggi C.M. *et al*: Epirubicin plasma and blood pharmacokinetics after single i.v. bolus in advanced cancer patients. *Drugs Exp Clin Res* 11(4):285-294, 1985.
101. Twelves C.J. *et al*: Clinical pharmacokinetics of epirubicin: the importance of liver biochemistry tests. *Br J Cancer* 66(4):765-769, 1992.
102. Camaggi CM, *et al*. Pharmacokinetic studies of 4'-epidoxorubicin in cancer patients with normal and impaired renal function and with hepatic metastases. *Cancer Treat Rep* 66(10):1819-1824, 1982.
103. Bauer KA, Levine M. Evaluation and management of the cancer patient with thrombosis. In: American Society of Clinical Oncology (ASCO) Educational Book. 223-233, 1999.
104. Murry LS, *et al*. The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced breast cancer: preliminary evidence of a potentially common interaction. *Clin Oncol (Royal College of Radiologists)* 10(1):35-38, 1998.
105. Plosker G.L. *et al*: Epirubicin. A review of its pharmacodynamic and -pharmacokinetic properties, and therapeutic use in cancer chemotherapy. *Drugs* 45 (5); 788-856, 1993.
106. El Helw LM, Lorigan PC, Robinson MH, *et al*. VEDex (vincristine, epirubicin dexamethasone): an effective and well-tolerated palliative chemotherapy regimen for non-Hodgkin's lymphoma. *Int J Oncol* 2000;16(4):777-782.
107. Bocchia M, Bigazzi C, Marconcini S, *et al*. Favorable impact of low-dose fludarabine plus epirubicin and cyclophosphamide regimen (FLEC) as treatment for low-grade non-Hodgkin's lymphomas. *Haematologica* 1999;84(8):716-720.
108. Aviles A, Nambo MJ, Talavera A, *et al*. Epirubicin (CEOP-Bleo) versus idarubicin (CIOP-Bleo) in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma: dose escalation studies. *Anti-Cancer Drugs* 1997;8(10):937-942.
109. Bertini M, Freilone R, Vitolo U, *et al*. The treatment of elderly patients with aggressive non-Hodgkin's lymphomas: feasibility and efficacy of an intensive multidrug regimen. *Leukemia & Lymphoma* 1996;22(5-6):483-493.
110. Lambertenghi Deliliers G, Butti C, *et al*. A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. *Haematologica* 1995;80(4):318-324.

111. Huan SD, Stewart DJ, Aitken SE, *et al.* Combination of epirubicin and cisplatin in hormone-refractory metastatic prostate cancer. *Am J Clin Oncol* 1999;22(5):471-474.
112. Veronesi A, Re GL, Foladore S, *et al.* Multidrug chemotherapy in the treatment of non-elderly patients with hormone-refractory prostatic carcinoma. A phase II study. North-Eastern Italian Oncology Group (GOCCNE). *Eur Urol* 1996;29(4):434-438.
113. Veronesi A, Lo Re G, Carbone A, *et al.* Multimodal treatment of locally advanced transitional cell bladder carcinoma in elderly patients. *Eur J Cancer* 1994;30A(7):918-920.
114. Quoix EA, Giaccone G, Jassem J, *et al.* Epirubicin in previously untreated patients with small cell lung cancer: a phase II study by the EORTC Lung Cancer Cooperative Group. *Eur J Cancer* 1992;28A(10):1667-1670.
115. Kouroussis C, Alexopoulos A, Giannakakis T, *et al.* A phase I/II study of docetaxel and epirubicin in advanced breast cancer (ABC). *Proc Annu Meet Am Soc Clin Oncol* 1999;18:A446.
116. Kataja V, Maenpae H, Heikkinen M, *et al.* A phase I/II study of docetaxel (Taxotere) in combination with epirubicin and 5-fluorouracil (DEF) as first line chemotherapy in patients with advanced breast cancer (ABC). *Proc Annu Meet Am Soc Clin Oncol* 1999;18:A444.
117. Delecroix V, Dieras V, Viens P, *et al.* Gemzar and epirubicin in patients with metastatic breast cancer (MBC): Preliminary results of a phase I study. *Proc Annu Meet Am Soc Clin Oncol* 1998;17:A520.
118. Lehnert M, Mross K, Schueller J, *et al.* Phase II trial of dexverapamil and epirubicin in patients with non-responsive metastatic breast cancer. *Br J Cancer* 1998;77(7):1155-1163.
119. Neri B, Pacini P, Bartalucci S, *et al.* Epirubicin high dose therapy in advanced breast cancer: preliminary clinical data. *Int J Clin Pharmacol Ther Toxicol* 1989;27:388-391.
120. Piccart MJ, Bruning P, Wildiers J, *et al.* An EORTC pilot study of filgrastim (recombinant human granulocyte colony stimulating factor) as support to a high dose-intensive epirubicin cyclophosphamide regimen in chemotherapy-naïve patients with locally advanced or metastatic breast cancer. *Ann Oncol* 1995;6(7):673-677.
121. Andre T, Louvet C, Ychou M, *et al.* Docetaxel – Epirubicin as second-line treatment for patients with advanced gastric cancer. *Proc Annu Meet Am Soc Clin Oncol* 1999;18:A1062.
122. Jakobsen P, Steiness E, Bastholt L, *et al.* Multiple-dose pharmacokinetics of epirubicin at four different dose levels: Studies in patients with metastatic breast cancer. *Cancer Chemother Pharmacol* 1991;28(1):63-68.
123. Deesen PE, Leyland-Jones B. Sensitive and specific determination of the anthracycline analog 4'-epidoxorubicin and its metabolites by high pressure liquid chromatography. *Drug Metab Dispos* 1984;12(1):9-13.
124. Rajala P, *et al.* Perioperative single dose instillation of Epirubicin or interferon-alpha after transurethral resection for the prophylaxis of primary superficial bladder cancer recurrence: A

- prospective randomized multicenter study – Finnbladder III long-term results. *J Urol* 2002; 168(3): 981-985.
125. Ali El-Dein B., *et al.* Single-dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transurethral resection of pTa and pT1 transitional-cell bladder tumours: a prospective, randomized controlled study. *Br J. Urology* 1997;79(5): 731-735.
 126. Ali El-Dein B., *et al.* Intravesical epirubicin versus doxorubicin for superficial bladder tumors (stages pTa and pT1): a randomized prospective study. *Journal of Urology* 1997;158(1): 68-74.
 127. Subar, Milayna, MD. Clinical Expert Report. Epirubicin for intravesical administration. October, 2005.
 128. Levine Mark, MD (Principal Investigator). Cooperative Clinical Trial of Intensive CEF Versus Standard CMF as Adjuvant Therapy for Breast Carcinoma in Premenopausal and Perimenopausal Patients with Histologically Involved Axillary Nodes (CTN 068103-999). 10-year Follow-up Report of the Trial MA-5. Pfizer Inc. FINAL 9 April, 2004.
 129. Levine M, *et al.* Randomized Trial Comparing Cyclophosphamide, Epirubicin, and Fluorouracil With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer: Update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. *Journal of Clinical Oncology*, Vol 23, No 22 (August), 2005: pp. 5166-5170.
 130. Bonnetterre Prof. J (Coordinating Investigator). Adjuvant Breast Cancer Treatment Trial in premenopausal, perimenopausal, and postmenopausal women with positive axillary nodes: 10 year results. 10-Year Follow-up Report of the Trial GFEA 05. Pfizer Inc. FINAL March 22, 2004.
 131. Bonnetterre J, *et al.* Long-Term Cardiac Follow-Up in Relapse-Free Patients After Six Courses of Fluorouracil, Epirubicin, and Cyclophosphamide, With Either 50 or 100 mg of Epirubicin, As Adjuvant Therapy for Node-Positive Breast Cancer: French Adjuvant Study Group. *Journal of Clinical Oncology*, Vol 22, No 15 (August), 2004: pp. 3070-3079.
 132. Ryberg M, Nielsen D, Skovsgaard T, Hansen J, Jensen BV, Dombernowsky P. Cardiotoxicity: An Analysis of 469 Patients With Metastatic Breast Cancer. *Journal of Clinical Oncology*, Vol 16, No 11 (November), 1998: pp. 3502-3508.
 133. Rogers, David DM, FRCP, FRCPC. Epirubicin Secondary Leukemia Monitoring Plan: Updated Analysis to December 31, 2001, Pfizer Inc., 20 December 2004.
 134. Tjuljandin SA, Doig RG, Sobol MM, *et al.* Pharmacokinetics and toxicity of two schedules of high dose epirubicin. *Cancer Res* 1990; 50:5095-5101.
 135. Poggesi, Italo, D Chem. Evaluation of pharmacokinetic interactions between epirubicin and taxanes. Pfizer, Inc. April 6, 2005.
 136. Podesta, Arturo, DVM, Independent Senior Toxicologist. Epirubicin Abbreviated Expert Statement on the Toxicopharmacological (Pre-Clinical) Documentation, February 2002.
 137. Podesta, Arturo, DVM, Independent Senior Toxicologist. Epirubicin Expert Statement on the Toxicopharmacological (Pre-Clinical) Documentation, October 2004.

138. Colombo G. Viscosity Change with Temperature of Epirubicin Hydrochloride Injection. November 2003 – In-house study (PNU-159378) d0624091.
139. Marini, G. Clinical Expert Statement on Intravesical Administration for Bladder Tumors, dated 7 March 2006 Pfizer Inc.
140. Marini, G. Clinical Expert Statement on Intravesical Administration, dated 6 March 2006 Pfizer Inc.
141. Lincoff A, Puccio D. A Clinical Expert Report to support revisions to the Core Data Sheet for Anthracyclines. Safety & Risk Management, Pfizer Inc. October 2008.
142. Lincoff A, Racanelli T. A Clinical Expert Report to support revisions to the epirubicin Core Data Sheet. Safety & Risk Management, Pfizer Inc. October 2008.
143. 2.5 Clinical Overview. Epirubicin Core Data Sheet Revision (May 2011). Sepsis, Haemorrhage, Pneumonia, and Other Safety Concepts.
144. 2.5. Clinical Overview to support revisions to the epirubicin Core Data Sheet, February 2014.
145. Module 2.5 Clinical Overview To Assign the Frequency Category to the Adverse Drug Reactions Under Section 4.8, Undesirable Effects, of the Core Data Sheet May 2016.
146. 2.5 Clinical Overview Update to section 4.4 Special Warnings and Precautions for Epirubicin Core Data Sheet, October 2018.
147. 2.5 Clinical Overview to Support the Updates to Section 4.4 Special warnings and precautions for use and Section 4.6 Fertility, pregnancy and lactation of the Core Data Sheet, December 2020.