

Epirubicin Hydrochloride Injection

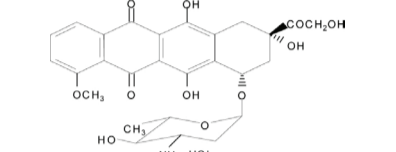


SAGENT

- WARNING**
- Severe local tissue necrosis will occur if there is extravasation during administration. See PRECAUTIONS. Epirubicin must not be given by the intramuscular or subcutaneous route.
 - Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin or clinically after therapy is terminated. The probability of developing clinically evident CHF is estimated as approximately 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 increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m²; this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with epirubicin hydrochloride injection may occur at lower cumulative doses whether or not cardiac risk factors are present.
 - Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The cumulative risk of developing treatment-related AML or myelodysplastic syndrome (MDS), in 7110 patients with breast cancer who received adjuvant treatment with epirubicin-containing regimens, was estimated as 0.27% at 3 years, 0.46% at 5 years, and 0.55% at 8 years.
 - Dosage should be reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).
 - Severe myelosuppression may occur.
 - Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Epirubicin hydrochloride injection is an anthracycline cytotoxic agent, intended for intravenous administration. Epirubicin hydrochloride injection is supplied as a sterile, clear, red solution and is available in colorless glass vials type I, containing 50 mg/25 mL and 200 mg/100 mL of epirubicin hydrochloride as a preservative-free, ready-to-use solution. Each milliliter of solution contains 2 mg of epirubicin hydrochloride. Inactive ingredients include sodium chloride, USP, and water for injection, USP. The pH of the solution has been adjusted to 3.0 with hydrochloric acid, NE. Epirubicin hydrochloride is the 4-epimer of doxorubicin and is a semi-synthetic derivative of daunorubicin. The chemical name is (8S)-10-(3-amino-2,3,6-trideoxy-L-oxabicyclo[3.3.1]non-7-yl)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-hydroxyacetyl)-methoxy-5,12-naphthoquinone hydrochloride. The active ingredient is a red-orange heptacyclic powder, with the empirical formula C₂₇H₃₁O₁₁ and a molecular weight of 579.95. The structural formula is as follows:



CLINICAL PHARMACOLOGY

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 nuclear DNA (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 resolution 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.

Pharmacokinetics

Epirubicin 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. Pharmacokinetic parameters for epirubicin following 5 to 10 minute, single-dose intravenous infusions of epirubicin hydrochloride at doses of 60 to 150 mg/m² in patients with solid tumors are shown in Table 1. The plasma concentration declined in a triphasic manner with mean half-lives for the alpha, beta, and gamma phases of about 3 minutes, 2.5 hours, and 33 hours, respectively.

| Dose ¹ (mg/m ²) | C ₁ ² (µg/mL) | C ₁ ³ (µg/mL) | t _{1/2} ¹ (hours) | t _{1/2} ² (hours) | t _{1/2} ³ (hours) | Cl _{CR} ⁴ (L/hour) | Cl _{CR} ⁵ (L/hour) |
|--|-------------------------------------|-------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|--|--|
| 60 | 5.7 ± 1.6 | 1.6 ± 0.2 | 35.3 ± 9 | 65 ± 8 | 21 ± 2 | | |
| 75 | 5.3 ± 1.5 | 1.7 ± 0.3 | 32.1 ± 5 | 83 ± 14 | 27 ± 11 | | |
| 120 | 9.0 ± 3.5 | 3.4 ± 0.7 | 33.7 ± 4 | 65 ± 13 | 23 ± 7 | | |
| 150 | 9.3 ± 2.9 | 4.2 ± 0.8 | 31.1 ± 6 | 69 ± 13 | 21 ± 7 | | |

- ¹Advanced solid tumor cancers, primarily of the lung
- ²N=6 patients per dose level
- ³Plasma concentration at the end of 6 to 10 minute infusion
- ⁴Area under the plasma concentration curve
- ⁵Half-life terminal phase
- ⁶Plasma clearance
- ⁷Steady state volume of distribution

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

Metabolism. Epirubicin is extensively and rapidly metabolized by the liver and is also metabolized by other organs and cells, including red blood cells. Four main metabolic routes have been identified: (1) reduction of the C-13 keto-group with the formation of the 13S-ethyloxy epirubicin; (2) conjugation of both the unchanged drug and epirubicin 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 reductive process with the formation of the 7-deoxy-doxorubicin aglycon and 7-deoxy-doxorubicinol aglycon. Epirubicin has *in vitro* cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicin 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 that 60% of the total radioactivity dose is excreted in urine (24%) and 36% in feces (24%), with 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

Age. A population analysis of plasma data from 36 cancer patients (13 males and 23 females, 20 to 73 years) showed that age affects plasma clearance of epirubicin in female patients. The predicted plasma clearance for a female patient of 70 years of age was about 35% lower than that for a female patient of 25 years of age. An insufficient number of males > 50 years of age were included in the study to draw conclusions about age-related alterations in clearance in males. Although a lower epirubicin starting dose does not appear necessary in elderly patients, and was not used in clinical trials, particular care should be taken in monitoring toxicity when epirubicin is administered to female patients > 70 years of age. (See PRECAUTIONS.)

Gender. In patients ≤ 50 years of age, mean clearance values in adult male and female patients were similar. The clearance of epirubicin is decreased in elderly women (see Pharmacokinetics in Special Populations—Age).

Pediatric. The pharmacokinetics of epirubicin in pediatric patients have not been evaluated.

Race. The influence of race on the pharmacokinetics of epirubicin has not been evaluated.

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 with hepatic dysfunction had serum AST (SGOT) levels above the upper limit of normal (median: 53 IU/L) and serum bilirubin levels (median: 0.5 mg/dL) and were given epirubicin 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 dose of 25 mg/m² (n=8). Their pharmacokinetics were compared to those of 16 patients with normal serum AST and bilirubin values, who received epirubicin doses of 12.5 to 120 mg/m². The median plasma clearance of epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Renal Impairment. No significant alterations in the pharmacokinetics of epirubicin or its major metabolite, epirubicinol, have been observed in patients with serum creatinine < 5 mg/dL. A 50% reduction in plasma clearance was reported in patients with serum creatinine ≥ 5 mg/dL. (See WARNINGS and DOSAGE AND ADMINISTRATION.) Patients on dialysis had not been studied.

Drug-Drug Interactions

Taxanes. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when given immediately following the taxane.

Cimetidine. Coadministration of cimetidine (400 mg twice daily for 7 days starting 5 days before chemotherapy) increased the mean AUC of epirubicin (100 mg/m²) by 50% and decreased its plasma clearance by 30%. (See PRECAUTIONS.)

Drugs metabolized by cytochrome P-450 enzymes. No systematic *in vitro* or *in vivo* evaluation has been performed to examine the potential for inhibition or induction by epirubicin of oxidative cytochrome P-450 isozymes.

CLINICAL STUDIES

Randomized, open-label, multicenter studies evaluated the use of epirubicin hydrochloride injection 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). Study MA-5 evaluated 120 mg/m² of epirubicin in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized patients 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, for only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptor and a histologic tumor grade of 2 or 3. A total of 1281 women participated in these studies. Patients with 14 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*

| Treatment Groups | Agents | Regimens |
|-------------------------------|--|--|
| MA-5 ¹ N=716 | CEF-120 (total, 6 cycles) ² | Cyclophosphamide Epirubicin Hydrochloride Fluorouracil |
| CEM ³ N=360 | Cyclophosphamide Methotrexate Fluorouracil | |
| GFEA-05 ⁴ N=565 | Fluorouracil Epirubicin Hydrochloride Cyclophosphamide | |
| FEC-50 ⁵ N=289 | Fluorouracil Epirubicin Hydrochloride Cyclophosphamide | |

- All women who underwent tamoxifen, breast irradiation was to be administered after completion of study chemotherapy.
- Patients also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or fluoroquinolone for the duration of their chemotherapy.
- 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 postmenopausal. 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 are presented in the text below and in Table 3. Results after 5 years of follow-up and results for endpoints were initially analyzed after 5 years of follow-up and are presented in Table 3. In Study MA-5, epirubicin-containing combination therapy (CEF-120) showed significantly longer RFS than CEM (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-containing CEF-120 regimen than for the CEM 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.

In Study GFEA-05, patients treated with the higher-dose epirubicin regimen (FEC-100) had a significantly longer 5-year RFS (estimated 63% 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. Results of follow-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. Although the trials were not powered for subgroup analyses, in the MA-5 study improvements in favor of FEC-120 vs. CEM were observed, in RFS and OS both in patients with 1 to 3 nodes positive and in those with ≥ 4 nodes positive. In the GFEA-05 study, improvements in RFS and OS were observed in both pre- and postmenopausal women treated with FEC-100 compared to FEC-50.

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

| | MA-5 Study | GFEA-05 Study | | |
|---|--------------|------------------|-----------------|----|
| CEF-120 N=356 | CEM N=360 | FEC-100 N=276 | FEC-50 N=289 | |
| RFS at 5 yrs (%) | 62 | 53 | 65 | 52 |
| Hazard ratio ¹ | 0.76 | 0.68 | | |
| 2-sided 95% CI | (0.60, 0.96) | (0.52, 0.89) | | |
| Log-rank Test (stratified) ² | (p=0.013) | (p=0.007) | | |
| OS at 5 yrs (%) | 77 | 70 | 76 | 65 |
| Hazard ratio ¹ | 0.71 | 0.69 | | |
| 2-sided 95% CI | (0.52, 0.98) | (0.51, 0.92) | | |
| Log-rank Test (stratified) ² | (p=0.043) | (p=0.007) | | |
| unstratified ³ | (p=0.13) | (p=0.007) | | |
| RFS at 10 yrs (%) | 51 | 44 | 49 | 43 |
| Hazard ratio ¹ | 0.78 | 0.78 | | |
| 2-sided 95% CI | (0.63, 0.96) | (0.62, 0.99) | | |
| Log-rank Test (stratified) ² | (p=0.017) | (p=0.040) | | |
| unstratified ³ | (p=0.023) | (p=0.009) | | |
| OS at 10 yrs (%) | 61 | 57 | 56 | 50 |
| Hazard ratio ¹ | 0.82 | 0.75 | | |
| 2-sided 95% CI | (0.65, 1.04) | (0.58, 0.96) | | |
| Log-rank Test (stratified) ² | (p=0.100) | (p=0.023) | | |
| unstratified ³ | (p=0.18) | (p=0.039) | | |

* Based on Kaplan-Meier estimates.
¹ Patients in MA-5 were stratified by nodal status (1 to 3, 4 to 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 [² Hazard ratio: CEM: CEF-120 in MA-5, FEC-50/FEC-100 in GFEA-05
³ Hazard ratio: CEM: 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

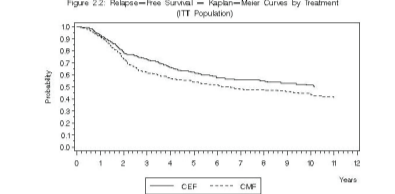


Figure 2. Overall Survival in Study MA-5

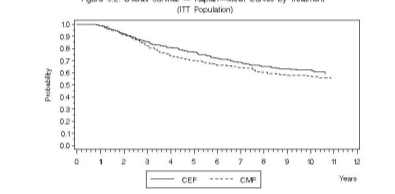


Figure 3. Relapse-Free Survival in Study GFEA-05

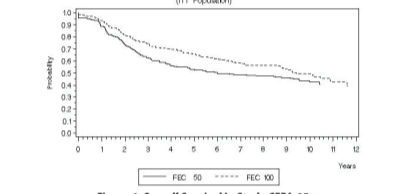
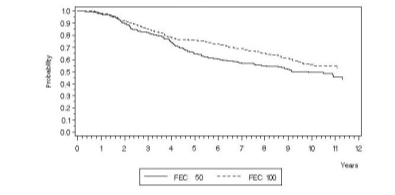


Figure 4. Overall Survival in Study GFEA-05



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

INDICATIONS AND USAGE

Epirubicin hydrochloride injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node involvement following resection of primary breast cancer.

CONTRAINDICATIONS

Patients should not be treated with epirubicin hydrochloride injection if they have any of the following conditions: baseline neutrophil count < 1500 cells/mm³; severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclins up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracediones; or severe hepatic dysfunction (see WARNINGS and DOSAGE AND ADMINISTRATION).

WARNINGS

Epirubicin hydrochloride injection should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Before beginning treatment with epirubicin, patients should be assessed for acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment. Also, initial treatment with epirubicin hydrochloride injection should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by ventricular ejection function (VEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression.

Supportive care may be necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to epirubicin.

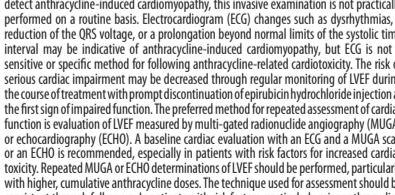
Hematologic Toxicity. A dose-dependent, reversible leukopenia and/or thrombocytopenia associated with epirubicin toxicity is associated with epirubicin. The most common acute dose-limiting toxicity of this drug. In most cases, the white blood cell (WBC) nadir is reached 10 to 14 days from drug administration. Leukopenia/neutropenia is usually transient, with WBC and neutrophil counts generally returning to normal values by Day 21 after drug administration. As with other anthracyclines, administration of epirubicin hydrochloride injection at the recommended dose in combination with cyclophosphamide and fluorouracil can produce severe leukopenia and neutropenia. Severe thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, septicemia, septic shock, hemorrhage, tissue hypoxia, symptomatic anemia, or death. If myelosuppressive complications occur, appropriate supportive measures (e.g., intravenous antibiotics, colony stimulating factors, transfusions) may be required. Myelosuppression requires careful monitoring. Total and differential WBC, red blood cell (RBC), and platelet counts should be assessed before and during each cycle of therapy with epirubicin hydrochloride injection.

Cardiac Function. Cardiotoxicity is a known early risk of anthracycline treatment. Anthracycline-induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of the syndrome consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as arteriovenular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of subsequent cardiotoxicity, an early clinical importance, and are generally not considered an indication for the suspension of epirubicin treatment. Delayed cardiac toxicity results from a characteristic cardiomyopathy that is manifested by reduced LVEF and/or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, peripheral edema, hepatomegaly, ascites, pleural effusion, gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy. This toxicity appears to be dependent on the cumulative dose of epirubicin hydrochloride injection and represents the cumulative dose-limiting toxicity of the drug. If it occurs, delayed cardiotoxicity usually develops in the course of therapy with epirubicin hydrochloride injection or within 2 to 3 months after completion of treatment, but later events (months to years after treatment termination) have been reported. In a 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. Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m² of epirubicin hydrochloride injection should be exceeded only with extreme caution. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracediones, concomitant use of other drugs with the ability to suppress cardiac conduction) may increase the risk of cardiac toxicity. Although not formally tested, it is probable that the toxicity of epirubicin and other anthracyclines or anthracediones is additive. Cardiac toxicity with epirubicin hydrochloride injection may occur at lower cumulative doses whether or not cardiac risk factors are present.

Although endomyocardial biopsy is recognized as the most sensitive diagnostic tool to detect anthracycline-induced cardiomyopathy, this invasive examination is not practically performed in a routine basis. Electrocardiogram (ECG) changes such as dysrhythmias, a prolonged QTc interval, or a prolongation beyond normal limits of the systolic interval may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be decreased through regular monitoring of LVEF during the course of therapy with epirubicin hydrochloride injection. The use of echocardiography as the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan is recommended, especially in patients with risk factors for the syndrome. In addition, Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracedione therapy, the monitoring of cardiac function must be particularly strict and the risk-benefit of continuing treatment with epirubicin hydrochloride injection in patients with impaired cardiac function must be carefully evaluated.

Secondary Leukemia. The occurrence of secondary acute myelogenous leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. These leukemia cases can have a short 1 to 3 year latency period. 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 to 0.40) at 3 years, 0.46% (approximate 95% CI, 0.28 to 0.65) at 5 years, and 0.55% (approximate 95% CI, 0.33 to 0.78) at 8 years. The risk of developing AML/MDS increased with increasing epirubicin cumulative dose as shown in Figure 6.

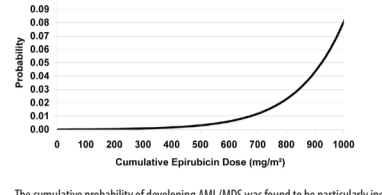
Figure 5. Risk of CHF in 9144 Patients treated with Epirubicin



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. Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m² of epirubicin hydrochloride injection should be exceeded only with extreme caution. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracediones, concomitant use of other drugs with the ability to suppress cardiac conduction) may increase the risk of cardiac toxicity. Although not formally tested, it is probable that the toxicity of epirubicin and other anthracyclines or anthracediones is additive. Cardiac toxicity with epirubicin hydrochloride injection may occur at lower cumulative doses whether or not cardiac risk factors are present.

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



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/m²) or cyclophosphamide (6,300 mg/m²), as shown in Table 4.

Table 4. 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 | Epirubicin Cumulative Dose > 720 mg/m ² | Epirubicin Cumulative Dose ≤ 720 mg/m ² | Epirubicin Cumulative Dose > 720 mg/m ² | |
| N=4760 | N=111 | N=890 | N=261 | |
| 3 | 0.12 (0.01 to 0.22) | 0.00 (0.00 to 0.00) | 0.12 (0.00 to 0.37) | 4.37 (1.06 to 7.67) |
| 5 | 0.25 (0.08 to 0.42) | 2.38 (0.00 to 6.99) | 0.31 (0.00 to 0.75) | 4.97 (2.06 to 8.05) |
| 8 | 0.37 (0.13 to 0.61) | 2.38 (0.00 to 6.99) | 0.31 (0.00 to 0.75) | 4.97 (2.06 to 7.87) |

Epirubicin hydrochloride is mutagenic, clastogenic, and carcinogenic in animals (see next section, Carcinogenesis, Mutagenesis and Impairment of Fertility).

Carcinogenesis, Mutagenesis & Impairment of Fertility. Treatment-related acute myelogenous leukemia has been reported in women treated with epirubicin-based adjuvant chemotherapy regimens (see above section, WARNINGS, Secondary Leukemia). Conventional long-term animal studies to evaluate the carcinogenic potential of epirubicin have not been conducted, but intravenous administration of a single 3 mg/kg epirubicin dose to female rats (about 0.2 times the maximum recommended human dose on a body surface area basis) approximately doubled the incidence of mammary tumors (primary fibroadenomas) observed at 1 year. Administration of 0.5 mg/kg epirubicin intravenously to rats (about 0.025 times the maximum recommended human dose on a body surface area basis) every 3 weeks for ten doses increased the incidence of subcutaneous fibromas in males over an 18-month observation period. In addition, subcutaneous administration of 0.75 or 1.0 mg/kg/day (about 0.015 times the maximum recommended human dose on a body surface area basis) to newborn rats for 4 days on both the first and tenth day after birth for a total of eight doses increased the incidence of animals with tumors compared to controls during a 24-month observation period.

Female rats were treated with epirubicin (0.5 mg/kg/day) in the presence or absence of metabolic activation and to mammalian cells (HPRT assay in V79 Chinese hamster lung fibroblasts) in the absence but not in the presence of metabolic activation. Epirubicin was clastogenic *in vitro* (chromosome aberrations in human lymphocytes) both in the presence and absence of metabolic activation and was also clastogenic *in vivo* (chromosome aberration in mouse bone marrow).

In fertility studies in rats, males were given epirubicin daily for 9 weeks and mated with females that were given epirubicin daily for 2 weeks prior to mating and through Day 7 of gestation. When 0.3 mg/kg/day (about 0.015 times the maximum recommended human single