

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use EPIRUBICIN HYDROCHLORIDE safely and effectively. See full prescribing information for EPIRUBICIN HYDROCHLORIDE.**

### Epirubicin hydrochloride injection

**Initial U.S. Approval: 1999**

<b>WARNING: SEVERE OR LIFE-THREATENING HEMATOLOGICAL AND OTHER ADVERSE REACTIONS</b>	
<i>See full prescribing information for complete boxed warning.</i>	
<ul style="list-style-type: none"><li>Severe local tissue necrosis associated with extravasation during administration (5.9)</li><li>Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF) (5.3)</li><li>Secondary acute myelogenous leukemia (AML) (5.4)</li><li>Reduce dosage in patients with impaired hepatic function (5.5)</li><li>Severe myelosuppression (5.2)</li><li>Administer only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents (5)</li></ul>	

### RECENT MAJOR CHANGES

Boxed Warning	09/2011
Dosage and Administration, Preparation and Administration (2.3)	09/2011
Warnings and Precautions, Injection-Related Reactions, Hematologic, Cardiac, Secondary Leukemia, Coadministration with Cimetidine, Pregnancy, Male Fertility and Reproductive Outcomes, Laboratory Testing, Inflammation following Irradiation (5.1, 5.2, 5.3, 5.4, 5.11, 5.12, 5.13, 5.14, 5.15)	09/2011
Drug Interactions, Cardioactive Compounds, Cimetidine, Other Cytotoxic Drugs, Radiation Therapy, Concomitant Therapies-Hepatic Function (7.1, 7.2, 7.3, 7.4, 7.5)	09/2011

### INDICATIONS AND USAGE

EPIRUBICIN HYDROCHLORIDE Injection is an anthracycline topoisomerase II inhibitor indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer (1.1).

### DOSAGE AND ADMINISTRATION

Administer intravenously in repeated 3- to 4-week cycles, either total dose on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle (2).

- The recommended starting dose of EPIRUBICIN HYDROCHLORIDE is 100 to 120 mg/m<sup>2</sup> Dosage reductions are possible when given in certain combinations (2.1).
- Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities (2.2).
- Reduce dose in patients with hepatic impairment (2.2, 8.6, 12.3).
- Consider lower doses in patients with severe renal impairment (2.2, 8.7, 12.3).

### DOSAGE FORMS AND STRENGTHS

Single use vials containing 2 mg Epirubicin hydrochloride per mL as a sterile, preservative-free, ready-to-use solution (50 mg/25 mL and 200 mg/100 mL) (3)

### CONTRAINDICATIONS

- Patients should not be treated with EPIRUBICIN HYDROCHLORIDE Injection if they have any of the following conditions: baseline neutrophil count < 1500 cells/mm<sup>3</sup> severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to Epirubicin hydrochloride, other anthracyclines, or anthracenediones; or severe hepatic dysfunction (4).
- The occurrence of secondary acute myelogenous leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines (5.4).
  - Serum total bilirubin and AST levels should be evaluated before and during treatment with EPIRUBICIN HYDROCHLORIDE. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients. Patients with severe hepatic impairment have not been evaluated (5.5).
  - Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine >5 mg/dL. Patients undergoing dialysis have not been studied (5.6).
  - EPIRUBICIN HYDROCHLORIDE may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of highly chemosensitive neoplastic cells (tumor-lysis syndrome) (5.7).
  - Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including EPIRUBICIN HYDROCHLORIDE, may result in serious or fatal infections (5.8).
  - Venous sclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Extravasation of EPIRUBICIN HYDROCHLORIDE during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Facial flushing, as well as local erythematous streaking along the vein, may be indicative of excessively rapid administration. It may precede local phlebitis or thrombophlebitis. Patients administered the 120-mg/m<sup>2</sup> regimen of EPIRUBICIN HYDROCHLORIDE as a component of combination chemotherapy should also receive prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole (e.g., Septra®, Bactrim®) or a fluoroquinolone (5.9).
  - EPIRUBICIN HYDROCHLORIDE is emetogenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of EPIRUBICIN HYDROCHLORIDE, particularly when given in conjunction with other emetogenic drugs (5.10).
  - Administration of EPIRUBICIN HYDROCHLORIDE after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation (5.11)
  - Thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of EPIRUBICIN HYDROCHLORIDE (5.12).
  - EPIRUBICIN HYDROCHLORIDE can cause fetal harm when administered to a pregnant woman. Advise women of potential risk to the fetus (5.12).

### ADVERSE REACTIONS

- In early breast cancer, acute adverse events occurring in ≥10% of patients are leucopenia, neutropenia, anemia, thrombocytopenia, amenorrhea, lethargy, nausea/vomiting, mucositis, diarrhea, infection, conjunctivitis/keratitis, alopecia, local toxicity and rash/itch (6).
- Long term adverse events occurring at a frequency of 1-2% are asymptomatic drops in LVEF and CHF and secondary leukemia (6).

**To report SUSPECTED ADVERSE REACTIONS,** Cipla Ltd, at 1-866-604-3268 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Do not administer Epirubicin hydrochloride in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (7.1).
- Stop Cimetidine during treatment with EPIRUBICIN HYDROCHLORIDE (7.2).

### USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue nursing prior to taking EPIRUBICIN HYDROCHLORIDE (8.3).
- Pediatric Use: Safety and effectiveness of EPIRUBICIN HYDROCHLORIDE in pediatric patients have not been established. Pediatric patients may be at greater risk for anthracycline-induced acute manifestations of cardiotoxicity and for chronic CHF (8.4).
- Geriatric Use: Care should be taken in monitoring toxicity when EPIRUBICIN HYDROCHLORIDE is administered to female patients ≥ 70 years of age. (8.5)

### See 17 for PATIENT COUNSELING INFORMATION

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## FULL PRESCRIBING INFORMATION

**WARNING: RISK OF TISSUE NECROSIS, CARDIAC TOXICITY, SECONDARY ACUTE MYELOGENOUS LEUKEMIA, AND MYELOSUPPRESSION**

- Severe local tissue necrosis will occur if there is extravasation during administration. EPIRUBICIN HYDROCHLORIDE must not be given by the intramuscular or subcutaneous route *[see Warnings and Precautions (5.9)]*.
- Cardiac toxicity, including fatal congestive heart failure (CHF), may occur either during therapy with EPIRUBICIN HYDROCHLORIDE or months to years after termination of therapy. The probability of developing clinically evident CHF is estimated as approximately 0.9% at a cumulative dose of 550 mg/m<sup>2</sup>, 1.6% at 700 mg/m<sup>2</sup>, and 3.3% at 900 mg/m<sup>2</sup>. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m<sup>2</sup>. The risk of developing CHF increases rapidly with increasing total cumulative doses of EPIRUBICIN HYDROCHLORIDE in excess of 900 mg/m<sup>2</sup>; 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 anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with EPIRUBICIN HYDROCHLORIDE may occur at lower cumulative doses whether or not cardiac risk factors are present *[see Warnings and Precautions (5.3)]*.
- Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including Epirubicin hydrochloride. 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 HYDROCHLORIDE-containing regimens, was estimated as 0.27% at 3 years, 0.46% at 5 years, and 0.55% at 8 years *[see Warnings and Precautions (5.4)]*.
- Severe myelosuppression may occur *[see Warnings and Precautions (5.2)]*.

### 1 INDICATIONS AND USAGE

EPIRUBICIN HYDROCHLORIDE Injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

### 2 DOSAGE AND ADMINISTRATION

When possible, to reduce the risk of developing cardiotoxicity in patients receiving EPIRUBICIN HYDROCHLORIDE after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, EPIRUBICIN HYDROCHLORIDE-based therapy should be delayed until the other agents have cleared from the circulation *[see Warnings and Precautions (5.3)]*. Administer EPIRUBICIN HYDROCHLORIDE Injection by intravenous infusion. Give EPIRUBICIN HYDROCHLORIDE in repeated 3- to 4-week cycles. The total dose of EPIRUBICIN HYDROCHLORIDE may be given on Day 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. The recommended dosages of EPIRUBICIN HYDROCHLORIDE are as follows:

#### 2.1 Recommended Dose

The recommended dose of EPIRUBICIN HYDROCHLORIDE is 100 to 120 mg/m<sup>2</sup>. The following regimens are recommended:

CEF-120:	Cyclophosphamide	75 mg/m <sup>2</sup> PO D 1-14
	EPIRUBICIN HYDROCHLORIDE	60 mg/m <sup>2</sup> IV D 1, 8
	5-Fluorouracil	500 mg/m <sup>2</sup> IV D 1, 8
Repeated every 28 days for 6 cycles		
FEC-100:	5-Fluorouracil	500 mg/m <sup>2</sup>
	EPIRUBICIN HYDROCHLORIDE	100 mg/m <sup>2</sup>
	Cyclophosphamide	500 mg/m <sup>2</sup>

All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles

Patients administered the 120-mg/m<sup>2</sup> regimen of EPIRUBICIN HYDROCHLORIDE should receive prophylactic antibiotic therapy.

#### 2.2 Dose Modifications

EPIRUBICIN HYDROCHLORIDE dosage adjustments for hematologic and non-hematologic toxicities within a cycle of treatment, is based on nadir platelet counts <50,000/mm<sup>3</sup>, absolute neutrophil counts (ANC) <250/mm<sup>3</sup>, neutropenic fever, or Grades 3/4 nonhematologic toxicity. Reduce EPIRUBICIN HYDROCHLORIDE Day 1 dose in subsequent cycles to 75% of the Day 1 dose given in the current cycle. Delay Day 1 chemotherapy in subsequent courses of treatment until platelet counts are ≥100,000/mm<sup>3</sup>, ANC ≥1500/mm<sup>3</sup>, and nonhematologic toxicities have recovered to ≤ Grade 1.

#### Bone Marrow Dysfunction

Consider administering a lower starting dose (75-90 mg/m<sup>2</sup>) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration *[see Warnings and Precautions (5)]*. For patients receiving a divided dose of EPIRUBICIN HYDROCHLORIDE (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm<sup>3</sup> and ANC is 1000 to 1499/mm<sup>3</sup>. If Day 8 platelet counts are <75,000/mm<sup>3</sup>, ANC <1000/mm<sup>3</sup>, or Grades 3/4 nonhematologic toxicity has occurred, omit the Day 8 dose.

#### Hepatic Impairment

Recommendations regarding use of EPIRUBICIN HYDROCHLORIDE in patients with hepatic impairment are not available because patients with hepatic abnormalities were not included in the adjuvant trials *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*. In patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions are recommended:

- Bilirubin 1.2 to 3 mg/dL or AST 2 to 4 times upper limit of normal 1/2 of recommended starting dose
- Bilirubin > 3 mg/dL or AST > 4 times upper limit of normal 1/4 of recommended starting dose

#### Renal Impairment

While no specific dose recommendation can be made based on the limited available data in patients with renal impairment, consider lower doses in patients with severe renal impairment (serum creatinine > 5 mg/dL) *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*.

#### 2.3 Preparation and Administration Precautions

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 2 to a maximum of 4 hours equilibration at controlled room temperature (15-25°C).

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Procedures for proper handling and disposal of anticancer drugs should be used when handling and preparing EPIRUBICIN HYDROCHLORIDE. Several guidelines on this subject have been published.<sup>1-4</sup> *[see References (15)]*.

#### Protective Measures

- Take the following protective measures when handling EPIRUBICIN HYDROCHLORIDE:
- Train personnel in appropriate techniques for reconstitution and handling.
- Exclude pregnant staff from working with this drug.
- Wear protective clothing: goggles, gloves, and disposable gloves and masks when handling EPIRUBICIN HYDROCHLORIDE.
- Define a designated area for syringe preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper.
- Place all items used for reconstitution, administration, or cleaning (including gloves) in high-risk, waste-disposal bags for high temperature incineration.
- Treat spillage or leakage with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. Place all contaminated and cleaning materials in high-risk, waste-disposal bags for incineration. Treat accidental contact with the skin or eyes immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Seek medical attention. Always wash hands after removing gloves.

#### Incompatibilities

Avoid prolonged contact with any solution of an alkaline pH as it will result in hydrolysis of the drug. Do not mix EPIRUBICIN HYDROCHLORIDE with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation. EPIRUBICIN HYDROCHLORIDE can be used in combination with other antitumor agents, but do not mix with other drugs in the same syringe.

#### Preparation of Infusion Solution

Administer EPIRUBICIN HYDROCHLORIDE into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution). Patients receiving initial therapy at the recommended starting doses of 100-120 mg/m<sup>2</sup> should generally have EPIRUBICIN HYDROCHLORIDE infused over 15-20 minutes. For patients who require lower EPIRUBICIN HYDROCHLORIDE starting doses due to organ dysfunction or who require modification of EPIRUBICIN HYDROCHLORIDE doses during therapy, the EPIRUBICIN HYDROCHLORIDE infusion time may be proportionally decreased, but should not be less than 3 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulitis, vesication, or tissue necrosis. 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein *[see Warnings and Precautions (5.9)]*. Use EPIRUBICIN HYDROCHLORIDE within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

#### 3 DOSAGE FORMS AND STRENGTHS

EPIRUBICIN HYDROCHLORIDE is provided in Single-use glass vials containing 2 mg Epirubicin hydrochloride per mL as a sterile, preservative-free, ready-to-use solution in the following sizes: 50 mg/25 mL and 200 mg/100 mL.

#### 4 CONTRAINDICATIONS

Patients should not be treated with EPIRUBICIN HYDROCHLORIDE Injection if they have any of the following conditions:

Severe myocardial insufficiency, recent myocardial infarction or severe arrhythmias *[see Warnings and Precautions (5.3)]*

Previous treatment with maximum cumulative dose of anthracyclines *[see Warnings and Precautions (5)]*.

Hypersensitivity to EPIRUBICIN HYDROCHLORIDE, other anthracyclines, or anthracenediones *[see Adverse Reactions (6.2)]*.

#### 5 WARNINGS AND PRECAUTIONS

Administer EPIRUBICIN HYDROCHLORIDE Injection only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Before beginning treatment with EPIRUBICIN HYDROCHLORIDE, patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment. Also, precede initial treatment with EPIRUBICIN HYDROCHLORIDE by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left ventricular ejection function (LVEF). Carefully monitor patients 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 HYDROCHLORIDE.

#### 5.1 Injection-Related Reactions

EPIRUBICIN HYDROCHLORIDE Injection is administered by intravenous infusion. Venous sclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Extravasation of EPIRUBICIN HYDROCHLORIDE during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Administer EPIRUBICIN HYDROCHLORIDE slowly into the tubing of a freely running intravenous infusion. Patients receiving initial therapy at the recommended starting doses of 100-120 mg/m<sup>2</sup> should generally have EPIRUBICIN HYDROCHLORIDE infused over 15-20 minutes. For patients who require lower EPIRUBICIN HYDROCHLORIDE starting doses due to organ dysfunction or who require modification of EPIRUBICIN HYDROCHLORIDE doses during therapy, the EPIRUBICIN HYDROCHLORIDE infusion time may be proportionally decreased, but should not be less than 3 minutes. *[see Dosage and Administration (2.3)]*. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. Immediately terminate infusion and restart in another vein if a burning or stinging sensation indicates perivenous infiltration. Perivenous infiltration may occur without causing pain. Facial flushing, as well as local erythematous streaking along the vein, may be indicative of excessively rapid administration. It may precede local phlebitis or thrombophlebitis. Give prophylactic antibiotic therapy to patients administered the 120-mg/m<sup>2</sup> regimen of EPIRUBICIN HYDROCHLORIDE as a component of combination chemotherapy *[see Clinical Studies (14.1) and Dosage and Administration 2.1)]*.

#### 5.2 Hematologic

Epirubicin hydrochloride can suppress bone marrow function as manifested by leukopenia, thrombocytopenia and anemia *[see Adverse Reactions (6.1)]*, and myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy *[see Dosage and Administration (2.2, 2.3)]*.

#### 5.3 Cardiac

Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of EPIRUBICIN HYDROCHLORIDE consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, 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 considered an indication for the suspension of EPIRUBICIN HYDROCHLORIDE 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, dependent 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 and represents the cumulative dose-limiting toxicity of the drug. If it occurs, delayed cardiotoxicity usually develops late in the course of therapy with EPIRUBICIN HYDROCHLORIDE or within 2 to 3 months after completion of treatment, but later events (several months to years after treatment termination) have been reported.

Given the risk of cardiomyopathy, exceed a cumulative dose of 900 mg/m<sup>2</sup> EPIRUBICIN HYDROCHLORIDE 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 anthracenediones, concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs, especially those with long half-lives (e.g., trastuzumab)) may increase the risk of EPIRUBICIN HYDROCHLORIDE cardiotoxicity *[see Drug Interaction (7.4) and Dosage and Administration (2)]*. Although not formally tested, it is probable that the toxicity of EPIRUBICIN HYDROCHLORIDE and other anthracyclines or anthracenediones is additive. Cardiac toxicity with EPIRUBICIN HYDROCHLORIDE 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 on a routine basis. ECG changes such as dysrhythmias, a reduction of the QRS voltage, or a prolongation beyond normal limits of the systolic time 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 treatment with prompt discontinuation of EPIRUBICIN HYDROCHLORIDE at 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 or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Perform repeated MUGA or ECHO determinations of LVEF, 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 anthracenedione use, the monitoring of cardiac function must be particularly strict and the risk-benefit of continuing treatment with EPIRUBICIN HYDROCHLORIDE in patients with impaired cardiac function must be carefully evaluated.

Do not administer EPIRUBICIN HYDROCHLORIDE in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving EPIRUBICIN HYDROCHLORIDE 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. Avoid EPIRUBICIN HYDROCHLORIDE-based therapy for up to 24 weeks after stopping trastuzumab when possible. If EPIRUBICIN HYDROCHLORIDE is used before this time, monitor cardiac function carefully *[see Dosage and Administration (2)]*.

#### 5.4 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 the anthracyclines have been escalated. These leukemias can have a short 1- to 3-year latency period.

EPIRUBICIN HYDROCHLORIDE is mutagenic, clastogenic, and carcinogenic in animals *[see Nonclinical Toxicology (13.1)]*.

#### 5.5 Hepatic

The major route of elimination of Epirubicin hydrochloride is the hepatobiliary system *[see Clinical Pharmacology (12.3)]*. Evaluate serum total bilirubin and AST levels before and during treatment with EPIRUBICIN HYDROCHLORIDE. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients *[see Dosage and Administration (2.2)]*. Patients with severe hepatic impairment have not been evaluated; therefore, do not use EPIRUBICIN HYDROCHLORIDE in this patient population.

#### 5.6 Renal

Assess serum creatinine before and during therapy. Dosage adjustment is necessary in patients with serum creatinine >5 mg/dL *[see Dosage and Administration (2.2)]*. Patients undergoing dialysis have not been studied.

#### 5.7 Tumor-Lysis Syndrome

As with other cytotoxic agents, EPIRUBICIN HYDROCHLORIDE may induce hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of highly chemosensitive neoplastic cells (tumor-lysis syndrome). Other metabolic abnormalities may also occur. While not generally a problem in patients with breast cancer, consider the potential for tumor-lysis syndrome in potentially susceptible patients and consider monitoring serum uric acid, potassium, calcium, phosphate, and creatinine immediately after initial chemotherapy administration. Hydration, urine alkalization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

#### 5.8 Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including Epirubicin hydrochloride, may result in serious or fatal infections. Avoid vaccination with a live vaccine in patients receiving EPIRUBICIN HYDROCHLORIDE. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

#### 5.9 Gastrointestinal

EPIRUBICIN HYDROCHLORIDE is emetogenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of EPIRUBICIN HYDROCHLORIDE, particularly when given in conjunction with other emetogenic drugs *[see Adverse Reactions (6)]*.

#### 5.10 Thrombophlebitis and Thromboembolic Phenomena

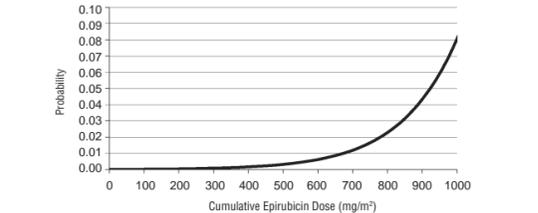
As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of EPIRUBICIN HYDROCHLORIDE.

#### 5.11 Coadministration with Cimetidine

Cimetidine increased the AUC of Epirubicin hydrochloride by 50%. Stop Cimetidine treatment during treatment with EPIRUBICIN HYDROCHLORIDE. *[see Clinical Pharmacology (12.3)]*

## 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 years. The risk of developing AML/MDS increased with increasing EPIRUBICIN HYDROCHLORIDE cumulative doses as shown in Figure 2.

**Figure 2. Risk of AML/MDS in 7110 Patients Treated with EPIRUBICIN HYDROCHLORIDE**


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/m<sup>2</sup>) or cyclophosphamide (6,300 mg/m<sup>2</sup>), as shown in Table 1.

**Table 1. 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 Cumulative Dose ≤6,300 mg/m <sup>2</sup>		Cyclophosphamide Cumulative Dose >6,300 mg/m <sup>2</sup>	
	EPIRUBICIN HYDROCHLORIDE Cumulative Dose ≤720 mg/m <sup>2</sup> N=4760	EPIRUBICIN HYDROCHLORIDE Cumulative Dose >720 mg/m <sup>2</sup> N=111	EPIRUBICIN HYDROCHLORIDE Cumulative Dose ≤720 mg/m <sup>2</sup> N=890	EPIRUBICIN HYDROCHLORIDE Cumulative Dose >720 mg/m <sup>2</sup> 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)

**Injection-Site Reactions** *[see Warnings and Precautions (5.9)].*

## 7 DRUG INTERACTIONS

### 7.1 Cardioactive Compounds

Do not administer Epirubicin hydrochloride in combination with other cardiotoxic agents unless the patient’s cardiac function is closely monitored. Patients receiving Epirubicin hydrochloride 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. Avoid Epirubicin hydrochloride-based therapy for up to 24 weeks after stopping trastuzumab when possible. If Epirubicin hydrochloride is used before this time, monitor cardiac function carefully *[see Dosage and Administration (2) and Warningsand Precautions (5.3)].*

Concomitant use of EPIRUBICIN HYDROCHLORIDE with other cardioactive compounds that could cause heart failure (e.g., calcium channel blockers), requires close monitoring of cardiac function throughout treatment.

### 7.2 Cimetidine

Cimetidine increases the exposure to Epirubicin hydrochloride *[see Clinical Pharmacology (12.3)]*. Stop Cimetidine during treatment withEPIRUBICIN HYDROCHLORIDE.

### 7.3 Other Cytotoxic Drugs

EPIRUBICIN HYDROCHLORIDE used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects.

### Paclitaxel:

The administration of Epirubicin hydrochloride immediately prior to or after paclitaxel increased the systemic exposure of Epirubicin hydrochloride, Epirubicin hydrochlorideoid and 7-deoxydoxorubicin hydrochloride *[see Clinical Pharmacology (12.3)]*.

### Docetaxel:

The administration of Epirubicin hydrochloride immediately prior to or after docetaxel did not have an effect on the systemic exposure of Epirubicin hydrochloride, but increased the systemic exposure of Epirubicin hydrochlorideoid and 7-deoxydoxorubicin aglycone *[see Clinical Pharmacology (12.3)]*.

### 7.4 Radiation Therapy

There are few data regarding the coadministration of radiation therapy and EPIRUBICIN HYDROCHLORIDE. In adjuvant trials of EPIRUBICIN HYDROCHLORIDE-containing CEF-120 or FEC-100 chemotherapies, breast irradiation was delayed until after chemotherapy was completed. This practice resulted in no apparent increase in local breast cancer recurrence relative to published accounts in the literature. A small number of patients received EPIRUBICIN HYDROCHLORIDE-based chemotherapy concomitantly with radiation therapy but had chemotherapy interrupted in order to avoid potential overlapping toxicities. It is likely that use of EPIRUBICIN HYDROCHLORIDE with radiotherapy may sensitize tissues to the cytotoxic actions of irradiation. Administration of EPIRUBICIN HYDROCHLORIDE after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation.

### 7.5 Concomitant Therapies-Hepatic Function

Epirubicin hydrochloride is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect Epirubicin hydrochloride metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity.

### 7.6 Drug/Laboratory Test Interactions

There are no known interactions between EPIRUBICIN HYDROCHLORIDE and laboratory tests.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category D. See ‘Warnings and Precautions’ section.

EPIRUBICIN HYDROCHLORIDE can cause fetal harm when administered to a pregnant woman. Administration of 0.8 mg/kg/day intravenously of Epirubicin hydrochloride to rats (about 0.04 times the maximum recommended single human dose on a body surface area basis) during Days 5 to 15 of gestation was embryotoxic (increased resorptions and post-implantation loss) and caused fetal growth retardation (decreased body weight), but was not teratogenic up to this dose. Administration of 2 mg/kg/day intravenously of Epirubicin hydrochloride to rats (about 0.1 times the maximum recommended single human dose on a body surface area basis) on Days 9 and 10 of gestation was embryotoxic (increased late resorptions, post-implantation losses, and dead fetuses; and decreased live fetuses), retarded fetal growth (decreased body weight), and caused decreased placental weight. This dose was also teratogenic, causing numerous external (anal atresia, misshapen tail, abnormal genital tubercle), visceral (primarily gastrointestinal, urinary, and cardiovascular systems), and skeletal (deformed long bones and girdles, rib abnormalities, irregular spinal ossification) malformations. Administration of intravenous Epirubicin hydrochloride to rabbits at doses up to 0.2 mg/kg/day (about 0.02 times the maximum recommended single human dose on a body surface area basis) during Days 6 to 18 of gestation was not embryotoxic or teratogenic, but a maternally toxic dose of 0.32 mg/kg/day increased abortions and delayed ossification. Administration of a maternally toxic intravenous dose of 1 mg/kg/day Epirubicin hydrochloride to rabbits (about 0.1 times the maximum recommended single human dose on a body surface area basis) on Days 10 to 12 of gestation induced abortion, but no other signs of embryofetal toxicity or teratogenicity were observed. When doses up to 0.5 mg/kg/day Epirubicin hydrochloride were administered to rat dams from Day 17 of gestation to Day 21 after delivery (about 0.025 times the maximum recommended single human dose on a body surface area basis), no permanent changes were observed in the development, functional activity, behavior, or reproductive performance of the offspring.

There are no adequate and well-controlled studies of EPIRUBICIN HYDROCHLORIDE in pregnant women. Two pregnancies have been reported in women taking Epirubicin hydrochloride. A 34-year-old woman, 28 weeks pregnant at her diagnosis of breast cancer, was treated with cyclophosphamide and Epirubicin hydrochloride every 3 weeks for 3 cycles. She received the last dose at 34 weeks of pregnancy and delivered a healthy baby at 35 weeks. A second 34-year-old woman with breast cancer

metastatic to the liver was randomized to FEC-50 but was removed from study because of pregnancy. She experienced a spontaneous abortion. If this drug 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. Women of childbearing potential should be advised to avoid becoming pregnant *[see Warnings and Precautions (5.12)]*.

### 8.3 Nursing Mothers

Epirubicin hydrochloride was excreted into the milk of rats treated with 0.50 mg/kg/day of Epirubicin hydrochloride during peri- and postnatal periods. It is not known whether this drug is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from EPIRUBICIN HYDROCHLORIDE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness of EPIRUBICIN HYDROCHLORIDE have not been established in pediatric patients. Pediatric patients may be at greater risk for anthracyclineinduced acute manifestations of cardiotoxicity and for chronic CHF. The pharmacokinetics of Epirubicin hydrochloride in pediatric patients have not been evaluated.

### 8.5 Geriatric Use

Although a lower starting dose of EPIRUBICIN HYDROCHLORIDE was not used in trials in elderly female patients, particular care should be taken in monitoring toxicity when EPIRUBICIN HYDROCHLORIDE is administered to female patients ≥ 70 years of age *[see Clinical Pharmacology (12.3)]*.

### 8.6 Hepatic Impairment

Epirubicin hydrochloride is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. Do not treat patients with severe hepatic impairment with EPIRUBICIN HYDROCHLORIDE. Reduce the starting dose for patients with less severe hepatic impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

### 8.7 Renal Impairment

No significant alterations in the pharmacokinetics of Epirubicin hydrochloride or its major metabolite, Epirubicin hydrochlorideoid, have been observed in patients with serum creatinine < 5 mg/dL. Consider lower doses in patients with severe renal impairment (serum creatinine > 5 mg/dL), as a reduction in plasma clearance was reported in these patients *[see, Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*. Patients on dialysis have not been studied.

## 10 OVERDOSAGE

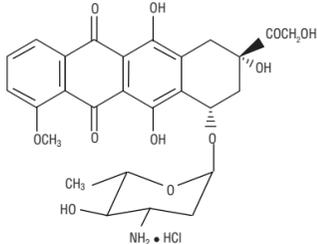
There is no known antidote for overdoses of EPIRUBICIN HYDROCHLORIDE. A 36-year-old man with non-Hodgkin’s lymphoma received a daily 95 mg/m<sup>2</sup> dose of EPIRUBICIN HYDROCHLORIDE Injection for 5 consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis, and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony-stimulating factors, and antifungal agents, and recovered completely. A 63-year-old woman with breast cancer and liver metastasis received a single 320 mg/m<sup>2</sup> dose of EPIRUBICIN HYDROCHLORIDE. She was hospitalized with hyperthermia and developed multiple organ failure (respiratory and renal), with lactic acidosis, increased lactate dehydrogenase, and anuria. Death occurred within 24 hours after administration of EPIRUBICIN HYDROCHLORIDE. Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m<sup>2</sup>. The observed adverse events in these patients were qualitatively similar to known toxicities of Epirubicin hydrochloride. Most of the patients recovered with appropriate supportive care.

If an overdose occurs, provide supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors, and intensive care as needed) until the recovery of toxicities. Delayed CHF has been observed months after anthracycline administration. Observe patients carefully over time for signs of CHF and provided with appropriate supportive therapy.

## 11 DESCRIPTION

EPIRUBICIN HYDROCHLORIDE Injection (Epirubicin hydrochloride injection) is an anthracycline cytotoxic agent, intended for intravenous administration. EPIRUBICIN HYDROCHLORIDE is supplied as a sterile, clear, red solution and is available in glass vials containing 50 and 200 mg 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, NF.

Epirubicin hydrochloride is the 4-epimer of doxorubicin and is a semi-synthetic derivative of daunorubicin. The chemical name is (8S-cis)-10[(3-amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12naphthacenedione hydrochloride. The active ingredient is a red-orange hygroscopic powder, with the empirical formulaC<sub>27</sub>H<sub>26</sub>NO<sub>11</sub>, HCl and a molecular weight of 579.95. The structural formula is as follows:



## 12 CLINICAL PHARMACOLOG

### 12.1 Mechanism of Action

Epirubicin hydrochloride 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 hydrochloride’s cytotoxic and/or antiproliferative properties have not been completely elucidated.

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

Epirubicin hydrochloride 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.

### 12.3 Pharmacokinetics

Epirubicin hydrochloride pharmacokinetics are linear over the dose range of 60 to 150 mg/m<sup>2</sup> and plasma clearance is not affected by the duration of infusion or administration schedule. Pharmacokinetic parameters for Epirubicin hydrochloride following 6- to 10-minute, single-dose intravenous infusions of EPIRUBICIN HYDROCHLORIDE at doses of 60 to 150 mg/m<sup>2</sup> in patients with solid tumors are shown in Table 4. 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.

**Table 4. Summary of Mean (±SD) Pharmacokinetic Parameters in Patients \* with Solid Tumors Receiving Intravenous EPIRUBICIN HYDROCHLORIDE 60 to 150 mg/m<sup>2</sup>**

Dose b (mg/m <sup>2</sup> )	C <sub>max</sub> c (µg/mL)	AUC d (µg•h/mL)	t <sub>1/2</sub> e (hours)	CL <sup>f</sup> (L/hour)	V <sub>ss</sub> g (L/kg)
60	5.7 ± 1.6	1.6 ± 0.2	35.3 ± 9	85 ± 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

\*Advanced solid tumor cancers, primarily of the lung

†N=6 patients per dose level

\*Plasma concentration at the end of 6 to 10 minute infusion

\*Area under the plasma concentration curve

\*Half-life of terminal phase

\*Plasma clearance

\*Steady state volume of distribution

### Distribution

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

### Metabolism

Epirubicin hydrochloride 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, Epirubicin hydrochlorideoid; (2) conjugation of both the unchanged drug and Epirubicin hydrochlorideoid 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. Epirubicin hydrochlorideoid has *in vitro* cytotoxic activity one-tenth that of Epirubicin hydrochloride. As plasma levels of Epirubicin hydrochlorideoid 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 hydrochloride 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 hydrochloride or its major metabolites in bile and urine, respectively, in the 4 days after treatment.

### Effect of 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 hydrochloride 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 HYDROCHLORIDE starting dose does not appear necessary in elderly female patients, and was not used in clinical trials, particular care should be taken in monitoring toxicity when EPIRUBICIN HYDROCHLORIDE is administered to female patients > 70 years of age *[see Patient Counseling Information (17)]*.

### Effect of Gender

In patients ≤ 50 years of age, mean clearance values in adult male and female patients were similar. The clearance of Epirubicin hydrochloride is decreased in elderly women.

### Effect of Race

The influence of race on the pharmacokinetics of Epirubicin hydrochloride has not been evaluated.

### Effect of Hepatic Impairment

Epirubicin hydrochloride 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/m<sup>2</sup>. 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/m<sup>2</sup> (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/m<sup>2</sup>. 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 *[see Dosage and Administration (2.2), and Warnings and Precautions (5.5)]*.

### Effect of Renal Impairment

No significant alterations in the pharmacokinetics of Epirubicin hydrochloride or its major metabolite, Epirubicin hydrochlorideoid, have been observed in patients with serum creatinine < 5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine ≥ 5 mg/dL *[see Warnings and Precautions (5.6) and Dosing and Administration (2.2)]*. Patients on dialysis have not been studied.

### Effect of Paclitaxel

The administration of paclitaxel (175-225 mg/m<sup>2</sup> as a 3-hour infusion) immediately before or after Epirubicin hydrochloride (90 mg/m<sup>2</sup> as bolus) caused variable increases in the systemic exposure (mean AUC) of Epirubicin hydrochloride ranging from 5% to 109%. At same doses of Epirubicin hydrochloride and paclitaxel, the mean AUC of the inactive metabolites of Epirubicin hydrochloride (Epirubicin hydrochlorideoid and 7-deoxy-aglycone) increased by 120% and 70%, respectively, when paclitaxel was immediately administered after Epirubicin hydrochloride. Epirubicin hydrochloride had no effect on the exposure of paclitaxel whether it was administered before or after paclitaxel.

### Effect of Docetaxel

The administration of docetaxel (70 mg/m<sup>2</sup> as 1-hour infusion) immediately before or after Epirubicin hydrochloride (90 mg/m<sup>2</sup> as bolus) had no effect on the systemic exposure (mean AUC) of Epirubicin hydrochloride. However, the mean AUC of Epirubicin hydrochlorideoid and 7-deoxy-aglycone increased by 22.5% and 95%, respectively, when docetaxel was immediately administered after Epirubicin hydrochloride compared to Epirubicin hydrochloride alone. Epirubicin hydrochloride had no effect on the exposure of docetaxel whether it was administered before or after docetaxel.

### Effect of Cimetidine

Coadministration of cimetidine (400 mg twice daily for 7 days starting 5 days before chemotherapy) increased the mean AUC of Epirubicin hydrochloride (100 mg/m<sup>2</sup>) by 50% and decreased its plasma clearance by 30%.

### 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 hydrochloride of oxidative cytochrome P-450 isoenzymes.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Conventional long-term animal studies to evaluate the carcinogenic potential of Epirubicin hydrochloride have not been conducted, but intravenous administration of a single 3.6 mg/kg Epirubicin hydrochloride 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 (primarily fibroadenomas) observed at 1 year. Administration of 0.5 mg/kg Epirubicin hydrochloride 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 24month observation period.

Epirubicin hydrochloride was mutagenic *in vitro* to bacteria (Ames test) either in the presence or absence of metabolic activation and to mammalian cells (HGPRt assay in V79 Chinese hamster lung fibroblasts) in the absence but not in the presence of metabolic activation. Epirubicin hydrochloride 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 hydrochloride daily for 9 weeks and mated with females that were given Epirubicin hydrochloride 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 dose on a body surface area basis) was administered to both sexes, no pregnancies resulted. No effects on mating behavior or fertility were observed at 0.1 mg/kg/day, but male rats had atrophy of the testes and epididymis, and reduced spermatogenesis. The 0.1 mg/kg/day dose also caused embryolethality. An increased incidence of fetal growth retardation was observed in these studies at 0.03 mg/kg/day (about 0.0015 times the maximum recommended human single dose on a body surface area basis). Multiple daily doses of Epirubicin hydrochloride to rabbits and dogs also caused atrophy of male reproductive organs. Single 20.5 and 12 mg/kg doses of intravenous Epirubicin hydrochloride caused testicular atrophy in mice and rats, respectively (both approximately 0.5 times the maximum recommended human dose on a body surface area basis). A single dose of 16.7 mg/kg Epirubicin hydrochloride caused

uterine atrophy in rats.

## 14 CLINICAL STUDIES

### 14.1 Adjuvant Treatment of Breast Cancer

Two randomized, open-label, multicenter studies evaluated the use of EPIRUBICIN HYDROCHLORIDE Injection 100 to 120 mg/m<sup>2</sup> in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m<sup>2</sup> of EPIRUBICIN HYDROCHLORIDE per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized premenopausal and perimenopausal women with one or more positive lymph nodes to an EPIRUBICIN HYDROCHLORIDE-containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m<sup>2</sup> of EPIRUBICIN HYDROCHLORIDE per course in combination with fluorouracil and cyclophosphamide (FEC-100). This study randomized pre- and postmenopausal 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 5 shows the treatment regimens that the patients received. Relapse-free survival was defined as 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 5. Treatment Regimens Used in Phase 3 Studies of Patients with Early Breast Cancer**

	Treatment Groups	Agent	Regimen
MA-5 <sup>a</sup>	<b>CEF-120</b> (total, 6 cycles) <sup>b</sup> N=356	Cyclophosphamide	75 mg/m <sup>2</sup> PO, d 1–14, q 28 days
N=716		EPIRUBICIN HYDROCHLORIDE	60 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days
	<b>CMF</b> (total, 6 cycles) N=360	Fluorouracil	500 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days
		Cyclophosphamide	100 mg/m <sup>2</sup> PO, d 1–14, q 28 days
		Methotrexate	40 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days
		Fluorouracil	600 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days
GFEA-05 <sup>a</sup>	<b>FEC-100</b> (total, 6 cycles) N=565	Fluorouracil	500 mg/m <sup>2</sup> IV, d 1, q 21 days
N=276		EPIRUBICIN HYDROCHLORIDE	100 mg/m <sup>2</sup> IV, d 1, q 21 days
		Cyclophosphamide	500 mg/m <sup>2</sup> IV, d 1, q 21 days
	<b>FEC-50</b> (total, 6 cycles) N=289	Fluorouracil	500 mg/m <sup>2</sup> IV, d 1, q 21 days