HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ELLENCE® (epirubicin hydrochloride injection)

Initial U.S. Approval: 1999

WARNING: SEVERE OR LIFE-THREATENING HEMATOLOGICAL AND OTHER ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

- Severe local tissue necrosis associated with extravasation during administration (5.9)
- Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF) (5.3)
- Secondary acute myelogenous leukemia (AML) (5.4)
- Reduce dosage in patients with impaired hepatic function (5.5)
- Severe myelosuppression (5.2)
- Administer only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents (5)

——————INDICATIONS AND USAGE——————

ELLENCE 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 ELLENCE is 100 to 120 mg/m^2. 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 ELLENCE Injection if they have any of the following conditions: baseline neutrophil count < 1500 cells/mm^3; cardiomyopathy and/or heart failure, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracenediones; or severe hepatic dysfunction (4).

——————WARNINGS AND PRECAUTIONS——————

- A dose-dependent, reversible leukopenia and/or neutropenia is the predominant manifestation of hematologic toxicity associated with ELLENCE and represents the most common acute dose-limiting toxicity (5.2).
- Cardiotoxicity is a known risk of anthracycline treatment and may be manifested by early (or acute) or late (delayed) events (5.3).
- 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 ELLENCE. 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).
- ELLENCE 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 ELLENCE, 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 ELLENCE 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^2 regimen of ELLENCE as a component of combination chemotherapy should also receive prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole (e.g., Septra®, Bactrim®) or a fluoroquinolone (5.9).
- ELLENCE is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of ELLENCE, particularly when given in conjunction with other emetigenic drugs (5.10).
- Administration of ELLENCE 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 ELLENCE (5.12).
- ELLENCE 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 leukopenia, neutropenia, anemia, thrombocytopenia, amenorrhea, lethargy, nausea/vomiting, mucositis, diarrhea, infection, conjunctivitis/keratitis, alopecia, local toxicity and rash/itch (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or ***www.fda.gov/medwatch***.

----------DRUG INTERACTIONS----------

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

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue nursing prior to taking ELLENCE (8.3).
- Pediatric Use: Safety and effectiveness of ELLENCE 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 ELLENCE is administered to female patients ≥ 70 years of age. (8.5)

See 17 for PATIENT COUNSELING INFORMATION Revised: 2/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

1. INDICATIONS AND USAGE

2. DOSAGE AND ADMINISTRATION

2.1. Recommended Dose
2.2. Dose Modifications
2.3. Preparation and Administration Precautions

3. DOSAGE FORMS AND STRENGTHS

4. CONTRAINDICATIONS

5. WARNINGS AND PRECAUTIONS

5.1. Injection-Related Reactions
5.2. Hematologic
5.3. Cardiac
5.4. Secondary Leukemia
5.5. Hepatic
5.6. Renal
5.7. Tumor-Lysis Syndrome
5.8. Immunosuppressant Effects/Increased Susceptibility to Infections
5.9. Gastrointestinal
5.10. Thrombophlebitis and Thromboembolic Phenomena
5.11. Coadministration with Cimetidine
5.12. Pregnancy
5.13. Male Fertility and Reproductive Outcomes
5.14. Laboratory Testing
5.15. Inflammation following Irradiation

6. ADVERSE REACTIONS

6.1. Clinical Trial Experience
6.2. Overview of Acute and Delayed Toxicities
6.3. Post-Marketing Experience

7. DRUG INTERACTIONS

7.1. Cardioactive Compounds
7.2. Cimetidine
7.3. Other Cytotoxic Drugs
7.4. Radiation Therapy
7.5. Concomitant Therapies-Hepatic Function
7.6. Drug/Laboratory Test Interactions

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy
8.3. Nursing Mothers
8.4. Pediatric Use
8.5. Geriatric Use
8.6. Hepatic Impairment
8.7. Renal Impairment

10. OVERDOSAGE

11. DESCRIPTION

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action
12.3. Pharmacokinetics

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14. CLINICAL STUDIES

14.1 Adjuvant Treatment of Breast Cancer

15. REFERENCES

16. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

**Sections or subsections omitted from the full prescribing information are not listed.*

FULL PRESCRIBING INFORMATION

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

1. Severe local tissue necrosis will occur if there is extravasation during administration. ELLENCE must not be given by the intramuscular or subcutaneous route *[see Warnings and Precautions (5.9)]*.
2. Cardiac toxicity, including fatal congestive heart failure (CHF), may occur either during therapy with ELLENCE 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^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of ELLENCE in excess of 900 mg/m^2; 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 ELLENCE may occur at lower cumulative doses whether or not cardiac risk factors are present *[see Warnings and Precautions (5.3)]*.
3. 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 ELLENCE-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)]*.
4. Severe myelosuppression may occur *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ELLENCE Injection is indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer *[see Clinical Studies (14.1)*.

2 DOSAGE AND ADMINISTRATION

When possible, to reduce the risk of developing cardiotoxicity in patients receiving ELLENCE after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, ELLENCE-based therapy should be delayed until the other agents have cleared from the circulation *[see Warnings and Precautions (5.3)]*.

Administer ELLENCE Injection by intravenous infusion. Give ELLENCE in repeated 3- to 4-week cycles. The total dose of ELLENCE 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 ELLENCE are as follows:

2.1 Recommended Dose

The recommended dose of ELLENCE is 100 to 120 mg/m^2. The following regimens are recommended:

CEF-120:	Cyclophosphamide	75 mg/m^2 PO D 1-14
	ELLENCE	60 mg/m^2 IV D 1, 8
	5-Fluorouracil	500 mg/m^2 IV D 1, 8
	Repeated every 28 days for 6 cycles	
FEC-100:	5-Fluorouracil	500 mg/m^2
	ELLENCE	100 mg/m^2
	Cyclophosphamide	500 mg/m^2
	All drugs administered intravenously on Day 1 and repeated every 21 days for 6 cycles	

Patients administered the 120-mg/m^2 regimen of ELLENCE should receive prophylactic antibiotic therapy.

2.2 Dose Modifications

ELLENCE dosage adjustments for hematologic and non-hematologic toxicities within a cycle of treatment, is based on nadir platelet counts <50,000/mm^3, absolute neutrophil counts (ANC) <250/mm^3, neutropenic fever, or Grades 3/4 nonhematologic toxicity. Reduce ELLENCE 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^3, ANC ≥1500/mm^3, and nonhematologic toxicities have recovered to ≤ Grade 1.

Bone Marrow Dysfunction
Consider administering a lower starting dose (75-90 mg/m^2) 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 ELLENCE (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm^3 and ANC is 1000 to 1499/mm^3. If Day 8 platelet counts are <75,000/mm^3, ANC <1000/mm^3, or Grades 3/4 nonhematologic toxicity has occurred, omit the Day 8 dose.

Hepatic Impairment
Recommendations regarding use of ELLENCE 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 (15-25ºC).

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 ELLENCE. Several guidelines on this subject have been published.[1-4] *[see References (15)]*.

Protective Measures
Take the following protective measures when handling ELLENCE:

- Train personnel in appropriate techniques for reconstitution and handling.
- Exclude pregnant staff from working with this drug.
- Wear protective clothing: goggles, gowns, and disposable gloves and masks when handling ELLENCE.
- 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 ELLENCE with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation.
ELLENCE 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 ELLENCE 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^2 should generally have ELLENCE infused over 15-20 minutes. For patients who require lower ELLENCE starting doses due to organ dysfunction or who require modification of ELLENCE doses during therapy, the ELLENCE 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 ELLENCE within 24 hours of first penetration of the rubber stopper. Discard any unused solution.

3 DOSAGE FORMS AND STRENGTHS

ELLENCE is provided in polypropylene single-use CYTOSAFE™ 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 ELLENCE Injection if they have any of the following conditions:

Cardiomyopathy and/or heart failure, 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 ELLENCE, other anthracyclines, or anthracenediones *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

Administer ELLENCE Injection only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Before beginning treatment with ELLENCE, patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment. Also, precede initial treatment with ELLENCE 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 ELLENCE.

5.1 Injection-Related Reactions

ELLENCE 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 ELLENCE during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis), and necrosis. Administer ELLENCE slowly into the tubing of a freely running intravenous infusion. Patients receiving initial therapy at the recommended starting doses of 100-120 mg/m^2 should generally have ELLENCE infused over 15-20 minutes. For patients who require lower ELLENCE starting doses due to organ dysfunction or who require modification of ELLENCE doses during therapy, the ELLENCE 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^2 regimen of ELLENCE as a component of combination chemotherapy *[see Clinical Studies (14.1) and Dosage and Administration 2.1)]*.

5.2 Hematologic

Ellence 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 ELLENCE 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 ELLENCE 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 ELLENCE and represents the cumulative dose-limiting toxicity of the drug. If it occurs, delayed cardiotoxicity usually develops late in the course of therapy with ELLENCE 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^2 ELLENCE 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 ELLENCE cardiotoxicity *[see Drug Interaction (7.4) and Dosage and Administration (2)]*. Although not formally tested, it is probable that the toxicity of ELLENCE and other anthracyclines or anthracenediones is additive. Cardiac toxicity with ELLENCE 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 ELLENCE 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 ELLENCE in patients with impaired cardiac function must be carefully evaluated.

Do not administer ELLENCE in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving ELLENCE 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 ELLENCE-based therapy for up to 24 weeks after stopping trastuzumab when possible. If ELLENCE 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.
ELLENCE is mutagenic, clastogenic, and carcinogenic in animals *[see Nonclinical Toxicology (13.1)]*.

5.5 Hepatic

The major route of elimination of epirubicin is the hepatobiliary system *[see Clinical Pharmacology (12.3)]*. Evaluate serum total bilirubin and AST levels before and during treatment with ELLENCE. 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 ELLENCE 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, ELLENCE 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 alkalinization, 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, may result in serious or fatal infections. Avoid vaccination with a live vaccine in patients receiving ELLENCE. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

5.9 Gastrointestinal

ELLENCE is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of ELLENCE, particularly when given in conjunction with other emetigenic drugs *[see Adverse Reactions (6.2)]*.

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 ELLENCE.

5.11 Coadministration with Cimetidine

Cimetidine increased the AUC of epirubicin by 50%. Stop Cimetidine treatment during treatment with ELLENCE
[see Clinical Pharmacology (12.3)].

5.12 Pregnancy

ELLENCE can cause fetal harm when administered to a pregnant woman. Epirubicin was embryolethal and teratogenic in rats and rabbits. There are no adequate and well-controlled studies of ELLENCE in pregnant women. 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 a fetus. Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods *[see Use In Specific Populations (8.1)]*.

5.13 Male Fertility and Reproductive Outcomes

Males with female sexual partners of childbearing potential should use contraception during and after cessation of ELLENCE therapy. ELLENCE may damage testicular tissue and spermatozoa. Possible sperm DNA damage raises concerns about loss of fertility and genetic abnormalities in fetuses. The duration of this effect is uncertain *[see Nonclinical Toxicology (13.1)]*.

5.14 Laboratory Testing

Assess blood counts, including absolute neutrophil counts, and liver function before and during each cycle of therapy with ELLENCE. Perform repeated evaluations of LVEF during therapy *[see Warnings and Precautions (5.5 and 5.6)]*.

5.15 Inflammation following Irradiation

As with other anthracyclines, administration of ELLENCE after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Integrated safety data are available from two studies (Studies MA-5 and GFEA-05) *[see Clinical Studies (14.1)]* evaluating ELLENCE-containing combination regimens in patients with early breast cancer. Of the 1260 patients treated in these studies, 620 patients received the higher-dose

ELLENCE regimen (FEC-100/CEF-120), 280 patients received the lower-dose ELLENCE regimen (FEC-50), and 360 patients received CMF. Serotonin-specific antiemetic therapy and colony-stimulating factors were not used in these trials. Clinically relevant acute adverse events are summarized in Table 1.

Table 1. Clinically Relevant Acute Adverse Events in Patients with Early Breast Cancer

Event	% of Patients					
	FEC-100/CEF-120 (N=620)		FEC-50 (N=280)		CMF (N=360)	
	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4
Hematologic						
Leukopenia	80.3	58.6	49.6	1.5	98.1	60.3
Neutropenia	80.3	67.2	53.9	10.5	95.8	78.1
Anemia	72.2	5.8	12.9	0	70.9	0.9
Thrombocytopenia	48.8	5.4	4.6	0	51.4	3.6
Endocrine						
Amenorrhea	71.8	0	69.3	0	67.7	0
Hot flashes	38.9	4.0	5.4	0	69.1	6.4
Body as a Whole						
Lethargy	45.8	1.9	1.1	0	72.7	0.3
Fever	5.2	0	1.4	0	4.5	0
Gastrointestinal						
Nausea/vomiting	92.4	25.0	83.2	22.1	85.0	6.4
Mucositis	58.5	8.9	9.3	0	52.9	1.9
Diarrhea	24.8	0.8	7.1	0	50.7	2.8
Anorexia	2.9	0	1.8	0	5.8	0.3
Infection						
Infection	21.5	1.6	15.0	0	25.9	0.6
Febrile neutropenia	NA	6.1	0	0	NA	1.1
Ocular						
Conjunctivitis/keratitis	14.8	0	1.1	0	38.4	0
Skin						
Alopecia	95.5	56.6	69.6	19.3	84.4	6.7
Local toxicity	19.5	0.3	2.5	0.4	8.1	0
Rash/itch	8.9	0.3	1.4	0	14.2	0
Skin changes	4.7	0	0.7	0	7.2	0

FEC & CEF = cyclophosphamide + ELLENCE + fluorouracil; CMF = cyclophosphamide + methotrexate + fluorouracil; NA = not available
Grade 1 or 2 changes in transaminase levels were observed but were more frequently seen with CMF than with CEF.

Delayed Events
Table 2 describes the incidence of delayed adverse events in patients participating in the MA-5 and GFEA-05 trials.

Table 2. Long-Term Adverse Events in Patients with Early Breast Cancer

Event	% of Patients		
	FEC-100/CEF-120 (N=620)	FEC-50 (N=280)	CMF (N=360)
Cardiac events			
Asymptomatic drops in LVEF	2.1*	1.4	0.8*
CHF	1.5	0.4	0.3
Leukemia			
AML	0.8	0	0.3

*In study MA-5, cardiac function was not monitored after 5 years.
Two cases of acute lymphoid leukemia (ALL) were also observed in patients receiving ELLENCE. However, an association between anthracyclines such as ELLENCE and ALL has not been clearly established.

6.2 Overview of Acute and Delayed Toxicities

Hematologic
Dose-dependent, reversible leukopenia and/or neutropenia is the predominant manifestation of hematologic toxicity associated with ELLENCE and represents 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 cytotoxic agents, ELLENCE at the recommended dose in combination with cyclophosphamide and fluorouracil can produce severe leukopenia and neutropenia. Severe thrombocytopenia and anemia may also occur.

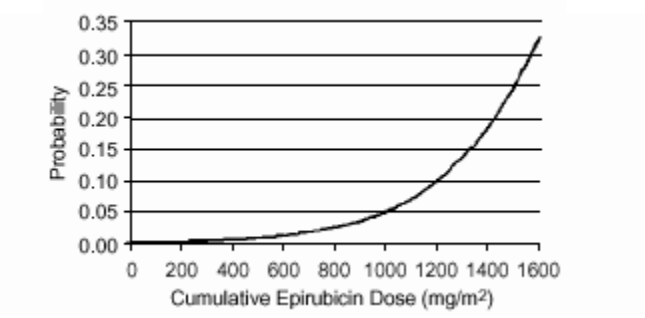
Clinical consequences of severe myelosuppression include fever, infection, septicemia, septic shock, hemorrhage, tissue hypoxia, symptomatic anemia, or death. If myelosuppressive complications occur, use appropriate supportive measures (e.g., intravenous antibiotics, colony-stimulating factors, transfusions). Myelosuppression requires careful monitoring. Assess total and differential WBC, red blood cell (RBC), and platelet counts before and during each cycle of therapy with ELLENCE *[see Warnings and Precautions (5.2)]*.

Gastrointestinal
A dose-dependent mucositis (mainly oral stomatitis, less often esophagitis) may occur in patients treated with ELLENCE. Clinical manifestations of mucositis may include a pain or burning sensation, erythema, erosions, ulcerations, bleeding, or infections. Mucositis 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. Hyperpigmentation of the oral mucosa may also occur. Nausea, vomiting, and occasionally diarrhea and abdominal pain can also occur. Severe vomiting and diarrhea may produce dehydration. Antiemetics may reduce nausea and vomiting; consider prophylactic use of antiemetics before therapy *[see Warnings and Precautions (5.10)]*.

Cutaneous and Hypersensitivity Reactions
Alopecia occurs frequently, but is usually reversible, with hair regrowth occurring within 2 to 3 months from the termination of therapy. Flushes, skin and nail hyperpigmentation, photosensitivity, and hypersensitivity to irradiated skin (radiation-recall reaction) have been observed. Urticaria and anaphylaxis have been reported in patients treated with ELLENCE; signs and symptoms of these reactions may vary from skin rash and pruritus to fever, chills, and shock.

Cardiovascular
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 ELLENCE (Figure 1). The estimated risk of ELLENCE-treated patients developing clinically evident CHF was 0.9% at a cumulative dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. The risk of developing CHF in the absence of other cardiac risk factors increased steeply after an ELLENCE cumulative dose of 900 mg/m^2 *[see Warnings and Precautions (5.4)]*.

Figure 1. Risk of CHF in 9144 Patients Treated with ELLENCE



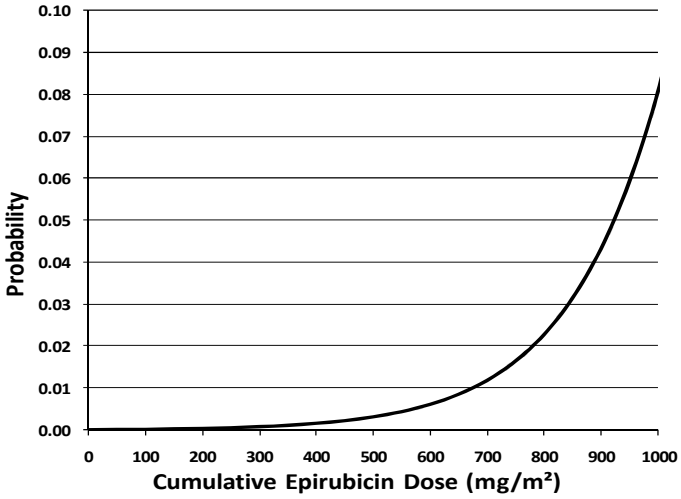
In another retrospective survey of 469 ELLENCE-treated patients with metastatic or early breast cancer, the reported risk of CHF was comparable to that observed in the larger study of over 9000 patients *[see Warnings and Precautions (5.3)]*.

Other serious drug-related cardiovascular adverse events that occurred during clinical trials with ELLENCE, administered in different indications, include ventricular tachycardia, AV block, bundle branch block, bradycardia and thromboembolism.

Secondary Leukemia

An analysis of 7110 patients who received adjuvant treatment with ELLENCE 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 ELLENCE cumulative doses as shown in Figure 2.

Figure 2. Risk of AML/MDS in 7110 Patients Treated with ELLENCE



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 ELLENCE (720 mg/m^2) or cyclophosphamide (6,300 mg/m^2), as shown in Table 3.

Table 3. Cumulative Probability of AML/MDS in Relation to Cumulative Doses of ELLENCE 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	
	ELLENCE Cumulative Dose ≤720 mg/m^2 N=4760	ELLENCE Cumulative Dose >720 mg/m^2 N=111	ELLENCE Cumulative Dose ≤720 mg/m^2 N=890	ELLENCE 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)

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

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of ELLENCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and infestations: sepsis, pneumonia

Immune system disorders: anaphylaxis

Metabolism and nutrition disorders: dehydration, hyperuricemia

Vascular disorders: shock, haemorrhage, embolism arterial, thrombophlebitis, phlebitis

Respiratory, thoracic and mediastinal disorders: pulmonary embolism

Gastrointestinal disorders: erosions, ulcerations, pain or burning sensation, bleeding, hyperpigmentation of the oral mucosa

Skin and subcutaneous tissue disorders: erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction), urticaria

Renal and urinary disorders: red coloration of urine for 1 to 2 days after administration

General disorders and administration site conditions: fever, chills

Injury, poisoning and procedural complications: chemical cystitis (following intravesical administration)

7 DRUG INTERACTIONS

7.1 Cardioactive Compounds

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

Concomitant use of ELLENCE 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 *[see Clinical Pharmacology (12.3)]*. Stop Cimetidine during treatment with ELLENCE.

7.3 Other Cytotoxic Drugs

ELLENCE used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal

effects.

Paclitaxel:
The administration of epirubicin immediately prior to or after paclitaxel increased the systemic exposure of epirubicin, epirubicinol and 7-deoxydoxorubicin aglycone *[see Clinical Pharmacology (12.3)]*.

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

7.4 Radiation Therapy

There are few data regarding the coadministration of radiation therapy and ELLENCE. In adjuvant trials of ELLENCE-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 ELLENCE-based chemotherapy concomitantly with radiation therapy but had chemotherapy interrupted in order to avoid potential overlapping toxicities. It is likely that use of ELLENCE with radiotherapy may sensitize tissues to the cytotoxic actions of irradiation. Administration of ELLENCE after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation.

7.5 Concomitant Therapies-Hepatic Function

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

7.6 Drug/Laboratory Test Interactions

There are no known interactions between ELLENCE and laboratory tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. See 'Warnings and Precautions' section.
ELLENCE can cause fetal harm when administered to a pregnant woman. Administration of 0.8 mg/kg/day intravenously of epirubicin 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 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 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 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 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 ELLENCE in pregnant women. Two pregnancies have been reported in women taking epirubicin. A 34-year-old woman, 28 weeks pregnant at her diagnosis of breast cancer, was treated with cyclophosphamide and epirubicin 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 was excreted into the milk of rats treated with 0.50 mg/kg/day of epirubicin 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 ELLENCE, 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 ELLENCE have not been established in pediatric patients. Pediatric patients may be at greater risk for anthracycline-induced acute manifestations of cardiotoxicity and for chronic CHF. The pharmacokinetics of epirubicin in pediatric patients have not been evaluated.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

Epirubicin 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 ELLENCE. 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 or its major metabolite, epirubicinol, 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.

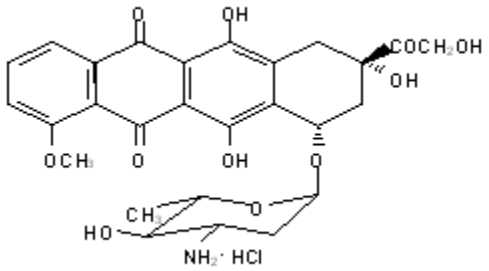
10 OVERDOSAGE

There is no known antidote for overdoses of ELLENCE. A 36-year-old man with non-Hodgkin's lymphoma received a daily 95 mg/m^2 dose of ELLENCE 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^2 dose of ELLENCE. 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 ELLENCE. Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m^2. The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. 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

ELLENCE Injection (epirubicin hydrochloride injection) is an anthracycline cytotoxic agent, intended for intravenous administration. ELLENCE is supplied as a sterile, clear, red solution and is available in polypropylene 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-5,12-naphthacenedione hydrochloride. The active ingredient is a red-orange hygroscopic powder, with the empirical formula $C_{27}H_{29}NO_{11}$ HCl and a molecular weight of 579.95. The structural formula is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis.

Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms.

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

12.3 Pharmacokinetics

Epirubicin pharmacokinetics are linear over the dose range of 60 to 150 mg/m^2 and plasma clearance is not affected by the duration of infusion or administration schedule. Pharmacokinetic parameters for epirubicin following 6- to 10-minute, single-dose intravenous infusions of ELLENCE at doses of 60 to 150 mg/m^2 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 [a] with Solid Tumors Receiving Intravenous ELLENCE 60 to 150 mg/m^2

Dose [b] (mg/m^2)	C_{max} [c] (µg/mL)	AUC [d] (µg•h/mL)	$t_{1/2}$ [e] (hours)	CL [f] (L/hour)	Vss [g] (L/kg)
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

[a] Advanced solid tumor cancers, primarily of the lung
[b] N=6 patients per dose level
[c] Plasma concentration at the end of 6 to 10 minute infusion
[d] Area under the plasma concentration curve
[e] Half-life of terminal phase
[f] Plasma clearance
[g] Steady 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 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.

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 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 ELLENCE 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 ELLENCE 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 is decreased in elderly women.

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

Effect of 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 ELLENCE doses of 12.5 to 90 mg/m^2. Patients in Group 2 had alterations in both serum AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an ELLENCE dose of 25 mg/m^2 (n=8). Their pharmacokinetics were compared to those of patients with normal serum AST and bilirubin values, who received ELLENCE doses of 12.5 to 120 mg/m^2. The median plasma clearance of epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated *[see Dosage and Administration (2.2), and Warnings and Precautions (5.5)]*.

Effect of Renal Impairment
No significant alterations in the pharmacokinetics of epirubicin or its major metabolite, epirubicinol, have been observed in patients with serum creatinine < 5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine ≥ 5 mg/dL *[see 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^2 as a 3-hour infusion) immediately before or after epirubicin (90 mg/m^2 as bolus) caused variable increases in the systemic exposure (mean AUC) of epirubicin ranging from 5% to 109%. At same doses of epirubicin and paclitaxel, the mean AUC of the inactive metabolites of epirubicin (epirubicinol and 7-deoxy-aglycone) increased by 120% and 70%, respectively, when paclitaxel was immediately administered after epirubicin. Epirubicin 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^2 as 1-hour infusion) immediately before or after epirubicin (90 mg/m^2 as bolus) had no effect on the systemic exposure (mean AUC) of epirubicin. However, the mean AUC of epirubicinol and 7-deoxy-aglycone increased by 22.5% and 95%, respectively, when docetaxel was immediately administered after epirubicin compared to epirubicin alone . Epirubicin 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 (100 mg/m^2) 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 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 have not been conducted, but intravenous administration of a single 3.6 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 (primarily 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.

Epirubicin 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 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 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 to rabbits and dogs also caused atrophy of male reproductive organs. Single 20.5 and 12 mg/kg doses of intravenous epirubicin 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 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 ELLENCE Injection 100 to 120 mg/m^2 in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m^2 of ELLENCE 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 ELLENCE-containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m^2 of ELLENCE 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[a]	**CEF-120** (total, 6 cycles)[b] N=356	Cyclophosphamide	75 mg/m^2 PO, d 1-14, q 28 days
N=716		ELLENCE	60 mg/m^2 IV, d 1 & 8, q 28 days
	CMF (total, 6 cycles) N=360	Fluorouracil	500 mg/m^2 IV, d 1 & 8, q 28 days
		Cyclophosphamide	100 mg/m^2 PO, d 1-14, q 28 days
		Methotrexate	40 mg/m^2 IV, d 1 & 8, q 28 days
GFEA-05[c]	**FEC-100** (total, 6 cycles)	Fluorouracil	500 mg/m^2 IV, d 1, q 21 days
N=565	N=276	ELLENCE	100 mg/m^2 IV, d 1, q 21 days
		Cyclophosphamide	500 mg/m^2 IV, d 1, q 21 days
	FEC-50 (total, 6 cycles)	Fluorouracil	500 mg/m^2 IV, d 1, q 21 days
	N=289	ELLENCE	50 mg/m^2 IV, d 1, q 21 days
	Tamoxifen 30 mg daily x	Cyclophosphamide	500 mg/m^2 IV, d 1, q 21 days
	3 years, postmenopausal		
	women, any receptor status		

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

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 were initially analyzed after up to 5 years of follow-up and these results are presented in the text below and in Table 6. Results after up to 10 years of follow-up are presented in Table 6. In Study MA-5, ELLENCE-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 ELLENCE-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.

In Study GFEA-05, patients treated with the higher-dose ELLENCE 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. 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 6.

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

Table 6. Efficacy Results from Phase 3 Studies of Patients with Early Breast Cancer*

	MA-5 Study		GFEA-05 Study	
	CEF-120 N=356	CMF N=360	FEC-100 N=276	FEC-50 N=289
RFS at 5 yrs (%)	62	53	65	52
Hazard ratio†	0.76		0.68	
2-sided 95% CI	(0.60, 0.96)		(0.52, 0.89)	
Logrank 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)	
Logrank 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)	
Logrank 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)	
Logrank Test stratified**	(p = 0.100) (unstratified p = 0.18)		(p = 0.023) (unstratified p = 0.039)	

*Based on Kaplan-Meier estimates
**Patients in MA-5 were stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by hormone receptor status (ER or PR positive (≥10 fmol), both negative (<10 fmol), or unknown status). Patients in GFEA-05 were stratified by nodal status (1-3, 4-10, and >10 positive nodes).
†Hazard ratio: CMF:CEF-120 in MA-5, FEC-50:FEC-100 in GFEA-05

The Kaplan-Meier curves for RFS and OS from Study MA-5 are shown in Figures 3 and 4 and those for Study GFEA-05 are shown in Figures 5 and 6.

Figure 3. Relapse-Free Survival in Study MA-5

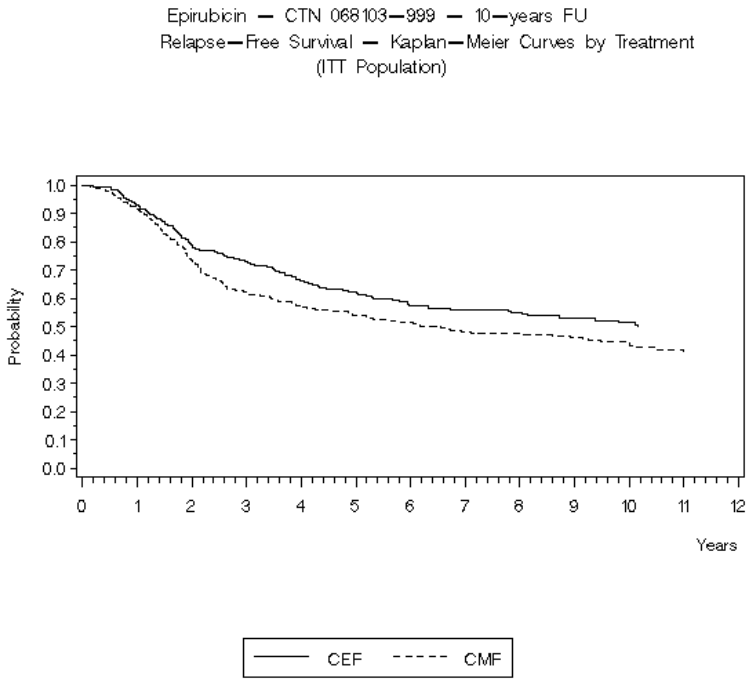


Figure 4. Overall Survival in Study MA-5

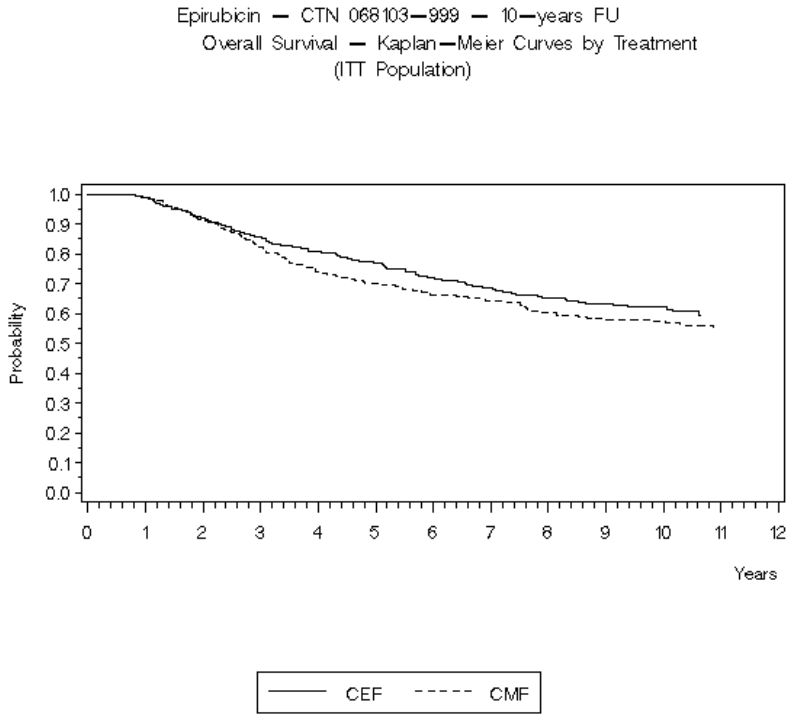


Figure 5. Relapse-Free Survival in Study GFEA-05

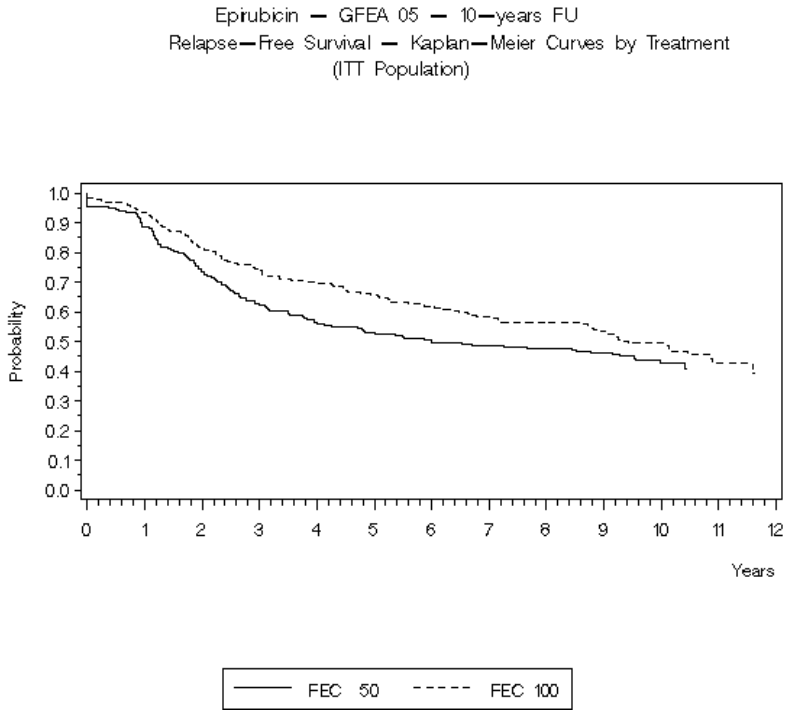
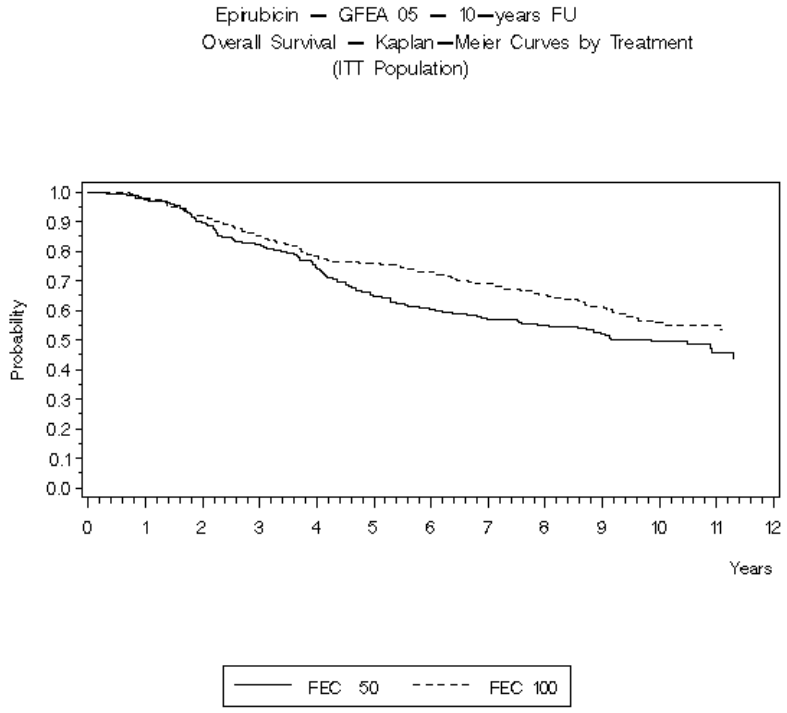


Figure 6. Overall Survival in Study GFEA-05



See Table 6 for statistics on 5 and 10 year analyses.

15 REFERENCES

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4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

ELLENCE Injection is available in polypropylene single-use CYTOSAFE™ vials containing 2 mg epirubicin hydrochloride per mL as a sterile, preservative-free, ready-to-use solution in the following strengths:

50 mg/25 mL single-use vial	NDC 0009-5091-01
200 mg/100 mL single-use vial	NDC 0009-5093-01

Store refrigerated between 2ºC and 8ºC (36ºF and 46ºF). Do not freeze. Protect from light.

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 (15-25ºC). Solution for injection should be used within 24 hours after removal from refrigeration.

17 PATIENT COUNSELING INFORMATION

Inform patients of the expected adverse effects of ELLENCE, including gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis), alopecia and potential neutropenic complications.

Patients should understand that there is a risk of irreversible myocardial damage associated with treatment with ELLENCE, as well as a risk of treatment-related leukemia.

Patients should consult their physician if vomiting, dehydration, fever, evidence of infection, symptoms of CHF, or injection-site pain occurs following therapy with ELLENCE.

Advise patients that their urine may appear red for 1 to 2 days after administration of ELLENCE and that they should not be alarmed.

Because ELLENCE may induce chromosomal damage in sperm, advise men undergoing treatment with ELLENCE to use effective contraceptive methods. Women treated with ELLENCE may develop irreversible amenorrhea, or premature menopause.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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