

1 **Elence<sup>®</sup>**  
2 **epirubicin hydrochloride injection**

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4 **DESCRIPTION**

5 ELLENCE Injection (epirubicin hydrochloride injection) is an anthracycline cytotoxic  
6 agent, intended for intravenous administration. ELLENCE is supplied as a sterile, clear,

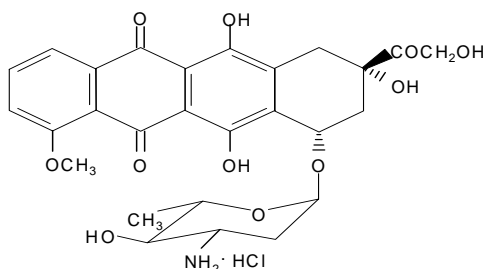
**WARNING**

1. Severe local tissue necrosis will occur if there is extravasation during administration (See PRECAUTIONS). Epirubicin must not be given by the intramuscular or subcutaneous route.
2. Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin 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 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 ELLENCE may occur at lower cumulative doses whether or not cardiac risk factors are present.
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 epirubicin-containing regimens, was estimated as 0.27% at 3 years, 0.46% at 5 years, and 0.55% at 8 years.
4. Dosage should be reduced in patients with impaired hepatic function (see DOSAGE AND ADMINISTRATION).
5. Severe myelosuppression may occur.
6. Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

7 red solution and is available in polypropylene vials containing 50 and 200 mg of  
8 epirubicin hydrochloride as a preservative-free, ready-to-use solution. Each milliliter of  
9 solution contains 2 mg of epirubicin hydrochloride. Inactive ingredients include sodium  
10 chloride, USP, and water for injection, USP. The pH of the solution has been adjusted to  
11 3.0 with hydrochloric acid, NF.

12 Epirubicin hydrochloride is the 4-epimer of doxorubicin and is a semi-synthetic

13 derivative of daunorubicin. The chemical name is (8*S*- *cis*)-10-[(3-amino-2,3,6-trideoxy-  
14  $\alpha$ -L- *arabino*-hexopyranosyl)oxy]-7,8,9,10- tetrahydro6,8,11-trihydroxy-8-  
15 (hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride. The active ingredient  
16 is a red-orange hygroscopic powder, with the empirical formula  $C_{27}H_{29}NO_{11}HCl$  and a  
17 molecular weight of 579.95. The structural formula is as follows:  
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### 23 CLINICAL PHARMACOLOGY

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

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

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

### 40 Pharmacokinetics

41 Epirubicin pharmacokinetics are linear over the dose range of 60 to 150 mg/m<sup>2</sup> and  
42 plasma clearance is not affected by the duration of infusion or administration schedule.  
43 Pharmacokinetic parameters for epirubicin following 6- to 10-minute, single-dose  
44 intravenous infusions of epirubicin at doses of 60 to 150 mg/m<sup>2</sup> in patients with solid  
45 tumors are shown in Table 1. The plasma concentration declined in a triphasic manner  
46 with mean half-lives for the alpha, beta, and gamma phases of about 3 minutes, 2.5 hours,  
47 and 33 hours, respectively.  
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53 **Table 1. Summary of Mean ( $\pm$ SD) Pharmacokinetic Parameters in Patients <sup>1</sup> with**  
 54 **Solid Tumors Receiving Intravenous Epirubicin 60 to 150 mg/m<sup>2</sup>**

Dose <sup>2</sup> (mg/m <sup>2</sup> )	C <sub>max</sub> <sup>3</sup> ( $\mu$ g/mL)	( $\mu$ g AUC <sup>4</sup> )	t 1/2 <sup>5</sup> (hours)	CL <sup>6</sup> (L/hour)	V <sub>ss</sub> <sup>7</sup> (L/kg)
60	5.7 $\pm$ 1.6	1.6 $\pm$ 0.2	35.3 $\pm$ 9	65 $\pm$ 8	21 $\pm$ 2
75	5.3 $\pm$ 1.5	1.7 $\pm$ 0.3	32.1 $\pm$ 5	83 $\pm$ 14	27 $\pm$ 11
120	9.0 $\pm$ 3.5	3.4 $\pm$ 0.7	33.7 $\pm$ 4	65 $\pm$ 13	23 $\pm$ 7
150	9.3 $\pm$ 2.9	4.2 $\pm$ 0.8	31.1 $\pm$ 6	69 $\pm$ 13	21 $\pm$ 7

55 <sup>1</sup> Advanced solid tumor cancers, primarily of the lung

56 <sup>2</sup> N=6 patients per dose level

57 <sup>3</sup> Plasma concentration at the end of 6 to 10 minute infusion

58 <sup>4</sup> Area under the plasma concentration curve

59 <sup>5</sup> Half-life of terminal phase

60 <sup>6</sup> Plasma clearance

61 <sup>7</sup> Steady state volume of distribution

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

67 **Metabolism.** Epirubicin is extensively and rapidly metabolized by the liver and is also  
68 metabolized by other organs and cells, including red blood cells. Four main metabolic  
69 routes have been identified:

70 (1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative,  
71 epirubicinol;  
72 (2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid; (3) loss  
73 of the amino sugar moiety through a hydrolytic process with the formation of the  
74 doxorubicin and doxorubicinol aglycones; and (4) loss of the amino sugar moiety through  
75 a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-  
76 doxorubicinol aglycone. Epirubicinol has in vitro cytotoxic activity one-tenth that of  
77 epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug,  
78 they are unlikely to reach in vivo concentrations sufficient for cytotoxicity. No significant  
79 activity or toxicity has been reported for the other metabolites.

80 **Excretion.** Epirubicin and its major metabolites are eliminated through biliary excretion  
81 and, to a lesser extent, by urinary excretion. Mass-balance data from 1 patient found about  
82 60% of the total radioactive dose in feces (34%) and urine (27%). These data are consistent  
83 with those from 3 patients with extrahepatic obstruction and percutaneous drainage, in  
84 whom approximately 35% and 20% of the administered dose were recovered as epirubicin  
85 or its major metabolites in bile and urine, respectively, in the 4 days after treatment.

#### 86 **Pharmacokinetics in Special Populations**

87 **Age.** A population analysis of plasma data from 36 cancer patients (13 males and 23  
88 females, 20 to 73 years) showed that age affects plasma clearance of epirubicin in female  
89 patients. The predicted plasma clearance for a female patient of 70 years of age was about  
90 35% lower than that for a female patient of 25 years of age. An insufficient number of  
91 males > 50 years of age were included in the study to draw conclusions about age-related  
92 alterations in clearance in males. Although a lower epirubicin starting dose does not appear  
93 necessary in elderly female patients, and was not used in clinical trials, particular care  
94 should be taken in monitoring toxicity when epirubicin is administered to female patients >  
95 70 years of age. (See PRECAUTIONS.)

96 **Gender.** In patients  $\leq$  50 years of age, mean clearance values in adult male and female  
97 patients were similar. The clearance of epirubicin is decreased in elderly women (see  
98 Pharmacokinetics in Special Populations - Age).

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

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

102 **Hepatic Impairment.** Epirubicin is eliminated by both hepatic metabolism and biliary  
103 excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the  
104 effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups.  
105 Patients in Group 1 (n=22) had serum AST (SGOT) levels above the upper limit of normal  
106 (median: 93 IU/L) and normal serum bilirubin levels (median: 0.5 mg/dL) and were given  
107 epirubicin doses of 12.5 to 90 mg/m<sup>2</sup>. Patients in Group 2 had alterations in both serum

108 AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an  
109 epirubicin dose of 25 mg/m<sup>2</sup> (n=8). Their pharmacokinetics were compared to those of  
110 patients with normal serum AST and bilirubin values, who received epirubicin doses of  
111 12.5 to 120 mg/m<sup>2</sup>. The median plasma clearance of epirubicin was decreased compared to  
112 patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in  
113 patients in Group 2. Patients with more severe hepatic impairment have not been evaluated.  
114 (See WARNINGS and DOSAGE AND ADMINISTRATION.)

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

#### 120 **Drug-Drug Interactions**

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

123 **Cimetidine.** Coadministration of cimetidine (400 mg twice daily for 7 days starting 5 days  
124 before chemotherapy) increased the mean AUC of epirubicin (100 mg/m<sup>2</sup>) by 50% and  
125 decreased its plasma clearance by 30% (see PRECAUTIONS).

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

#### 129 **CLINICAL STUDIES**

130 Two randomized, open-label, multicenter studies evaluated the use of ELLENCE  
131 Injection 100 to 120 mg/m<sup>2</sup> in combination with cyclophosphamide and fluorouracil for the  
132 adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of  
133 distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m<sup>2</sup> of epirubicin  
134 per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen).  
135 This study randomized premenopausal and perimenopausal women with one or more  
136 positive lymph nodes to an epirubicin-containing CEF-120 regimen or to a CMF regimen.  
137 Study GFEA-05 evaluated the use of 100 mg/m<sup>2</sup> of epirubicin per course in combination  
138 with fluorouracil and cyclophosphamide (FEC-100). This study randomized pre- and  
139 postmenopausal women to the FEC-100 regimen or to a lower-dose FEC-50 regimen. In  
140 the GFEA-05 study, eligible patients were either required to have ≥ 4 nodes involved with  
141 tumor or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-  
142 receptors and a histologic tumor grade of 2 or 3. A total of 1281 women participated in  
143 these studies. Patients with T4 tumors were not eligible for either study. Table 2 shows the  
144 treatment regimens that the patients received. The primary endpoint of the trials was  
145 relapse-free survival, ie, time to occurrence of a local, regional, or distant recurrence, or  
146 disease-related death. Patients with contralateral breast cancer, second primary malignancy  
147 or death from causes other than breast cancer were censored at the time of the last visit  
148 prior to these events.

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**Table 2. Treatment Regimens Used in Phase 3 Studies of Patients with Early Breast Cancer**

	Treatment Groups	Agent	Regimen
MA-5 <sup>1</sup> N=716	<b>CEF-120</b> (total, 6 cycles) <sup>2</sup> N=356  <b>CMF</b> (total, 6 cycles) N=360	Cyclophosphamide ELLENC Fluorouracil Cyclophosphamide Methotrexate Fluorouracil	75 mg/m <sup>2</sup> PO, d 1-14, q 28 days 60 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days 500 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days 100 mg/m <sup>2</sup> PO, d 1-14, q 28 days 40 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days 600 mg/m <sup>2</sup> IV, d 1 & 8, q 28 days
GFEA-05 <sup>3</sup> N=565	<b>FEC-100</b> (total, 6 cycles) N=276  <b>FEC-50</b> (total, 6 cycles) N=289 Tamoxifen 30 mg daily x 3 years, postmenopausal women, any receptor status	Fluorouracil ELLENC Cyclophosphamide Fluorouracil ELLENC Cyclophosphamide	500 mg/m <sup>2</sup> IV, d 1, q 21 days 100 mg/m <sup>2</sup> IV, d 1, q 21 days 500 mg/m <sup>2</sup> IV, d 1, q 21 days 500 mg/m <sup>2</sup> IV, d 1, q 21 days 50 mg/m <sup>2</sup> IV, d 1, q 21 days 500 mg/m <sup>2</sup> IV, d 1, 21 days

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<sup>1</sup> In women who underwent lumpectomy, breast irradiation was to be administered after completion of study chemotherapy.

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<sup>2</sup> Patients also received prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or fluoroquinolone for the duration of their chemotherapy.

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<sup>3</sup> All women were to receive breast irradiation after the completion of chemotherapy.

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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  $\geq 4$  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  $\geq 4$  involved lymph nodes. Demographic and tumor characteristics were well-balanced between treatment arms in each study.

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The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results for endpoints were initially analyzed after up to 5 years of follow-up and these results are presented in the text below and in Table 3. Results after up to 10 years of follow-up are presented in Table 3. In Study MA-5, epirubicin-containing combination therapy (CEF-120) showed significantly longer RFS than CMF (5-year estimates were 62% versus 53%, stratified logrank for the overall RFS p=0.013). The estimated reduction in the risk of relapse was 24% at 5 years. The OS was also greater for the epirubicin-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.

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In Study GFEA-05, patients treated with the higher-dose epirubicin regimen (FEC-100) had a significantly longer 5-year RFS (estimated 65% versus 52%, logrank for the overall

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176 RFS p=0.007) and OS (estimated 76% versus 65%, logrank for the overall survival  
 177 p=0.007) than patients given the lower dose regimen (FEC-50). The estimated reduction in  
 178 risk of relapse was 32% at 5 years.. The estimated reduction in the risk of death was 31%  
 179 at 5 years. Results of follow-up up to 10 years (median follow-up = 8.8 years and 8.3  
 180 years, respectively for Study MA-5 and Study GFEA05), are presented in Table 3.

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

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Table 3. 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
<b>RFS at 5 yrs (%)</b>	62	53	65	52
Hazard ratio <sup>†</sup>	0.76		0.68	
2-sided 95% CI	(0.60, 0.96)		(0.52, 0.89)	
Log-rank Test stratified**	(p = 0.013)		(p = 0.007)	
<b>OS at 5 yrs (%)</b>	77	70	76	65
Hazard ratio <sup>†</sup>	0.71		0.69	
2-sided 95% CI	(0.52, 0.98)		(0.51, 0.92)	
Log-rank Test stratified**	(p = 0.043) (unstratified p = 0.13)		(p = 0.007)	
<b>RFS at 10 yrs (%)</b>	51	44	49	43
Hazard ratio <sup>†</sup>	0.78		0.78	
2-sided 95% CI	(0.63, 0.96)		(0.62, 0.99)	
Log-rank Test stratified**	(p = 0.017) (unstratified p = 0.023)		(p = 0.040) (unstratified p = 0.09)	
<b>OS at 10 yrs (%)</b>	61	57	56	50
Hazard ratio <sup>†</sup>	0.82		0.75	
2-sided 95% CI	(0.65, 1.04)		(0.58, 0.96)	
Log-rank Test stratified**	(p = 0.100) (unstratified p = 0.18)		(p = 0.023) (unstratified p = 0.039)	
*Based on Kaplan-Meier estimates				
**Patients in MA-5 were stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by hormone receptor status (ER or PR positive ( $\geq 10$ 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).				
<sup>†</sup> Hazard ratio: CMF:CEF-120 in MA-5, FEC-50:FEC-100 in GFEA-05				

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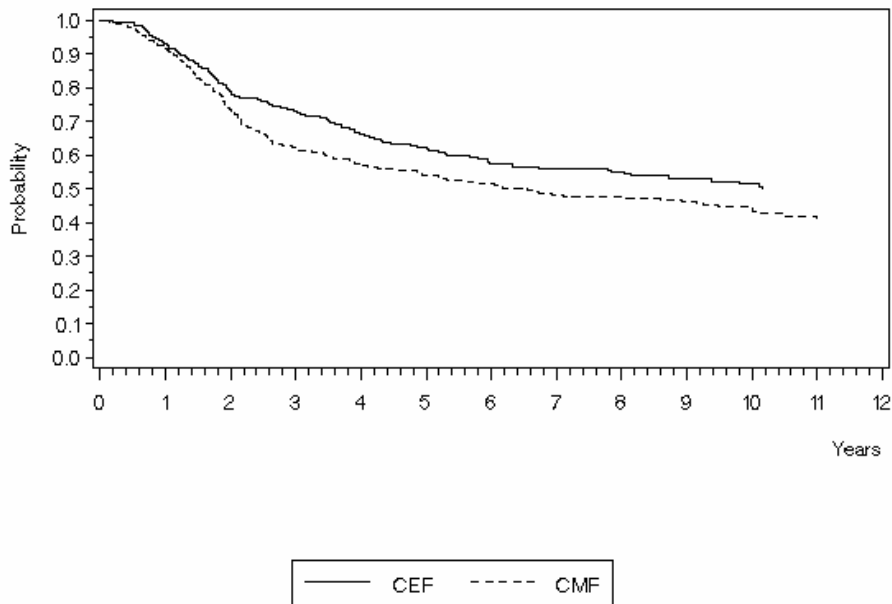
191 The Kaplan-Meier curves for RFS and OS from Study MA-5 are shown in Figures 1 and 2 and  
192 those for Study GFEA-05 are shown in Figures 3 and 4.

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

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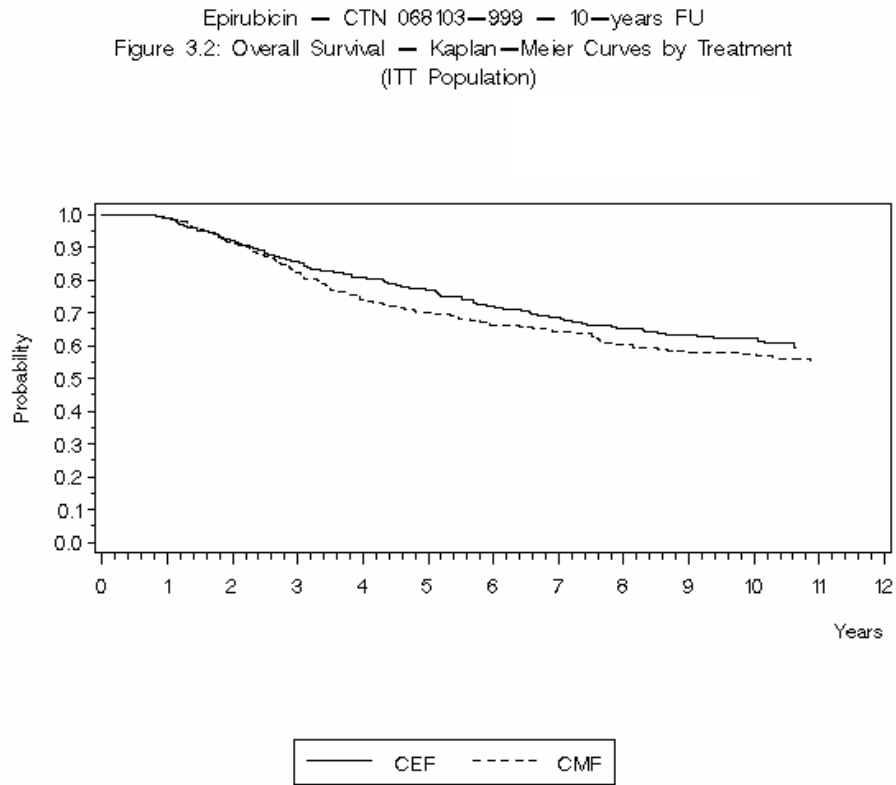
Epirubicin — CTN 068103-999 — 10-years FU  
Figure 2.2: Relapse-Free Survival — Kaplan-Meier Curves by Treatment  
(ITT Population)



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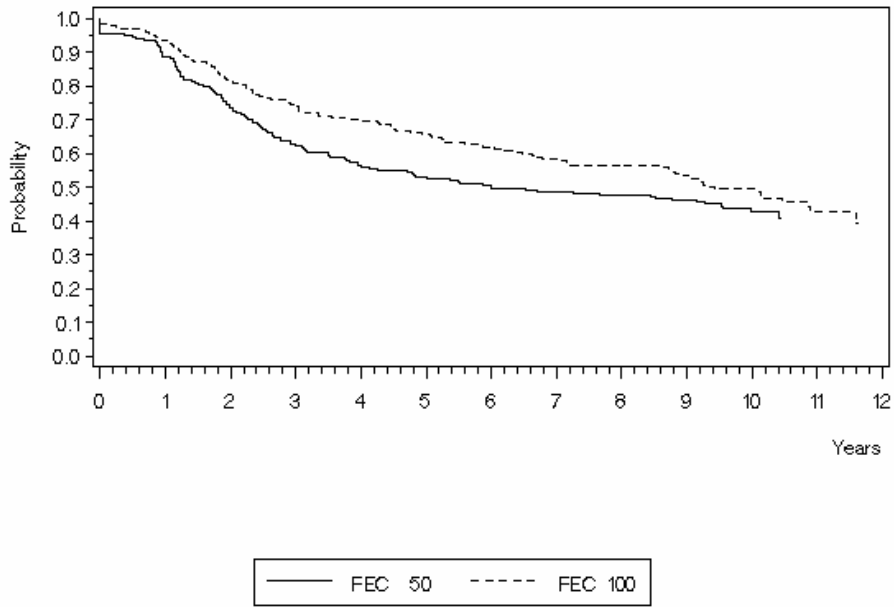


214 Figure 2. Overall Survival in Study MA-5  
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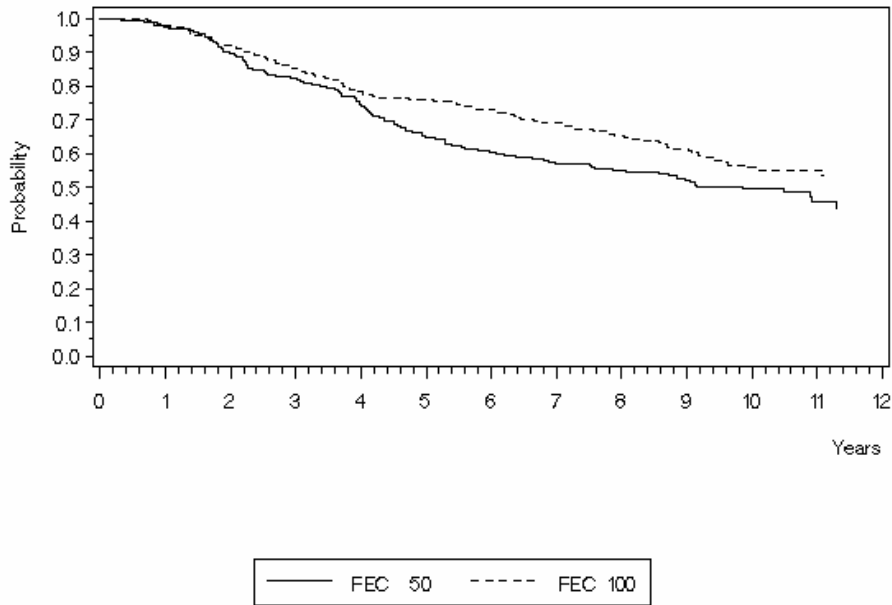
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218 Figure 3. Relapse-Free Survival in Study GFEA-05  
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Epirubicin — GFEA 05 — 10—years FU  
Figure 2.2: Relapse-Free Survival — Kaplan—Meier Curves by Treatment  
(ITT Population)



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222 Figure 4. Overall Survival in Study GFEA-005  
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Epirubicin — GFEA 05 — 10—years FU  
Figure 3.2: Overall Survival — Kaplan—Meier Curves by Treatment  
(ITT Population)



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225 See Table 3 for statistics on 5 and 10 year analyses.  
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### 227 **INDICATIONS AND USAGE**

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

### 230 **CONTRAINDICATIONS**

231 Patients should not be treated with ELLENCE Injection if they have any of the following  
232 conditions: baseline neutrophil count < 1500 cells/mm<sup>3</sup>; severe myocardial insufficiency,  
233 recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines  
234 up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines,  
235 or anthracenediones; or severe hepatic dysfunction (see WARNINGS and DOSAGE AND  
236 ADMINISTRATION).

### 237 **WARNINGS**

238 ELLENCE Injection should be administered only under the supervision of qualified  
239 physicians experienced in the use of cytotoxic therapy. Before beginning treatment with  
240 epirubicin, patients should recover from acute toxicities (such as stomatitis, neutropenia,  
241 thrombocytopenia, and generalized infections) of prior cytotoxic treatment. Also, initial  
242 treatment with ELLENCE should be preceded by a careful baseline assessment of blood  
243 counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as  
244 measured by left ventricular ejection function (LVEF). Patients should be carefully  
245 monitored during treatment for possible clinical complications due to myelosuppression.

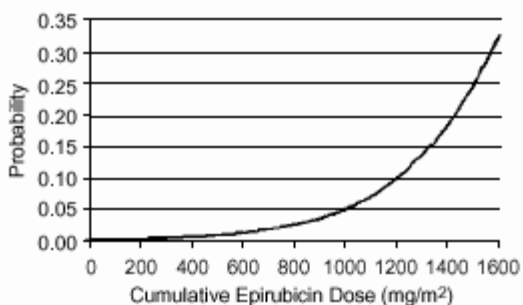
246 Supportive care may be necessary for the treatment of severe neutropenia and severe  
247 infectious complications. Monitoring for potential cardiotoxicity is also important,  
248 especially with greater cumulative exposure to epirubicin.

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

264 **Cardiac Function.** Cardiotoxicity is a known risk of anthracycline treatment.  
265 Anthracycline-induced cardiac toxicity may be manifested by early (or acute) or late  
266 (delayed) events. Early cardiac toxicity of epirubicin consists mainly of sinus tachycardia  
267 and/or ECG abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias,  
268 including premature ventricular contractions and ventricular tachycardia, bradycardia, as  
269 well as atrioventricular and bundle-branch block have also been reported. These effects do  
270 not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical  
271 importance, and are generally not considered an indication for the suspension of epirubicin  
272 treatment. Delayed cardiac toxicity results from a characteristic cardiomyopathy that is  
273 manifested by reduced LVEF and/or signs and symptoms of congestive heart failure (CHF)  
274 such as tachycardia, dyspnea, pulmonary edema, dependent edema, hepatomegaly, ascites,  
275 pleural effusion, gallop rhythm. Lifethreatening CHF is the most severe form of  
276 anthracycline-induced cardiomyopathy. This toxicity appears to be dependent on the  
277 cumulative dose of ELLENCE and represents the cumulative dose-limiting toxicity of the  
278 drug. If it occurs, delayed cardiotoxicity usually develops late in the course of therapy with  
279 ELLENCE or within 2 to 3 months after completion of treatment, but later events (several  
280 months to years after treatment termination) have been reported.

281 In a retrospective survey, including 9144 patients, mostly with solid tumors in advanced  
282 stages, the probability of developing CHF increased with increasing cumulative doses of  
283 ELLENCE (Figure 5). The estimated risk of epirubicin-treated patients developing  
284 clinically evident CHF was 0.9% at a cumulative dose of 550 mg/m<sup>2</sup>, 1.6% at 700 mg/m<sup>2</sup>,  
285 and 3.3% at 900 mg/m<sup>2</sup>. The risk of developing CHF in the absence of other cardiac risk  
286 factors increased steeply after an epirubicin cumulative dose of 900 mg/m<sup>2</sup>.

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



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

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Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m<sup>2</sup> ELLENCE should be exceeded only with extreme caution. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other drugs with the ability to suppress cardiac contractility) may increase the risk of cardiac toxicity. Although not formally tested, it is probable that the toxicity of epirubicin 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.

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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. Electrocardiogram (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. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or 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.

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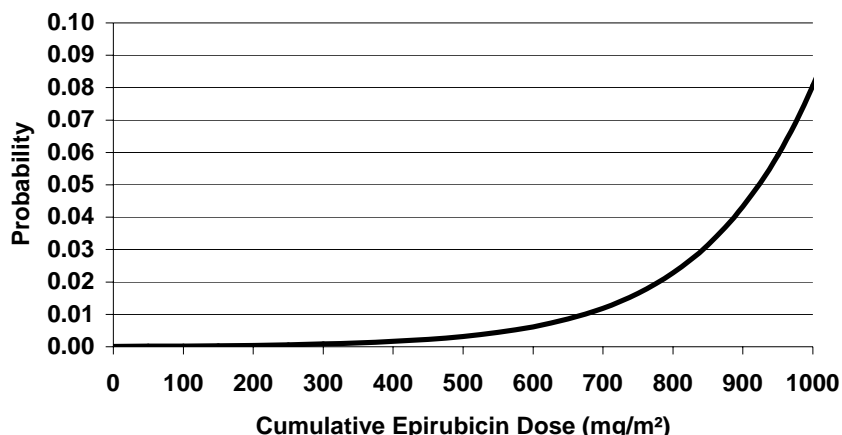
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**Secondary Leukemia.** The occurrence of secondary acute myelogenous leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines. Secondary leukemia is more common when such drugs are given in combination 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. An analysis of 7110 patients who received adjuvant treatment with epirubicin in controlled clinical trials as a component of poly-chemotherapy regimens for early breast cancer, showed a cumulative risk of secondary

325 acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) of about 0.27%  
326 (approximate 95% CI, 0.14-0.40) at 3 years, 0.46% (approximate 95% CI, 0.28-0.65) at 5  
327 years and 0.55% (approximate 95% CI, 0.33-0.78) at 8 years. The risk of developing  
328 AML/MDS increased with increasing epirubicin cumulative doses as shown in Figure 6.  
329

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



331 The cumulative probability of developing AML/MDS was found to be particularly  
332 increased in patients who received more than the maximum recommended cumulative dose  
333 of epirubicin (720 mg/m<sup>2</sup>) or cyclophosphamide (6,300 mg/m<sup>2</sup>), as shown in Table 4.  
334  
335

336 **Table 4. Cumulative probability of AML/MDS in relation to cumulative doses of**  
337 **epirubicin and cyclophosphamide**  
338

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 Cumulative Dose ≤720 mg/m <sup>2</sup> N=4760	Epirubicin Cumulative Dose >720 mg/m <sup>2</sup> N=111	Epirubicin Cumulative Dose ≤720 mg/m <sup>2</sup> N=890	Epirubicin 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)

339  
340  
341 ELLENCE is mutagenic, clastogenic, and carcinogenic in animals (see next section,  
342 Carcinogenesis, Mutagenesis and Impairment of Fertility).  
343 **Carcinogenesis, Mutagenesis & Impairment of Fertility.** Treatment-related acute  
344 myelogenous leukemia has been reported in women treated with epirubicin-based adjuvant  
345 chemotherapy regimens (see above section, WARNINGS, Secondary Leukemia).  
346 Conventional long-term animal studies to evaluate the carcinogenic potential of epirubicin

347 have not been conducted, but intravenous administration of a single 3.6 mg/kg epirubicin  
348 dose to female rats (about 0.2 times the maximum recommended human dose on a body  
349 surface area basis) approximately doubled the incidence of mammary tumors (primarily  
350 fibroadenomas) observed at 1 year. Administration of 0.5 mg/kg epirubicin intravenously  
351 to rats (about 0.025 times the maximum recommended human dose on a body surface area  
352 basis) every 3 weeks for ten doses increased the incidence of subcutaneous fibromas in  
353 males over an 18-month observation period. In addition, subcutaneous administration of  
354 0.75 or 1.0 mg/kg/day (about 0.015 times the maximum recommended human dose on a  
355 body surface area basis) to newborn rats for 4 days on both the first and tenth day after  
356 birth for a total of eight doses increased the incidence of animals with tumors compared to  
357 controls during a 24-month observation period.

358 Epirubicin was mutagenic in vitro to bacteria (Ames test) either in the presence or  
359 absence of metabolic activation and to mammalian cells (HGPRT assay in V79 Chinese  
360 hamster lung fibroblasts) in the absence but not in the presence of metabolic activation.  
361 Epirubicin was clastogenic in vitro (chromosome aberrations in human lymphocytes) both  
362 in the presence and absence of metabolic activation and was also clastogenic in vivo  
363 (chromosome aberration in mouse bone marrow).

364 In fertility studies in rats, males were given epirubicin daily for 9 weeks and mated with  
365 females that were given epirubicin daily for 2 weeks prior to mating and through Day 7 of  
366 gestation. When 0.3 mg/kg/day (about 0.015 times the maximum recommended human  
367 single dose on a body surface area basis) was administered to both sexes, no pregnancies  
368 resulted. No effects on mating behavior or fertility were observed at 0.1 mg/kg/day, but  
369 male rats had atrophy of the testes and epididymis, and reduced spermatogenesis. The 0.1  
370 mg/kg/day dose also caused embryoletality. An increased incidence of fetal growth  
371 retardation was observed in these studies at 0.03 mg/kg/day (about 0.0015 times the  
372 maximum recommended human single dose on a body surface area basis). Multiple daily  
373 doses of epirubicin to rabbits and dogs also caused atrophy of male reproductive organs.  
374 Single 20.5 and 12 mg/kg doses of intravenous epirubicin caused testicular atrophy in mice  
375 and rats, respectively (both approximately 0.5 times the maximum recommended human  
376 dose on a body surface area basis). A single dose of 16.7 mg/kg epirubicin caused uterine  
377 atrophy in rats.

378 Although experimental data are not available, ELLENCE could induce chromosomal  
379 damage in human spermatozoa due to its genotoxic potential. Men undergoing treatment  
380 with ELLENCE should use effective contraceptive methods. ELLENCE may cause  
381 irreversible amenorrhea (premature menopause) in premenopausal women.

382 **Liver Function.** The major route of elimination of epirubicin is the hepatobiliary system  
383 (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). Serum  
384 total bilirubin and AST levels should be evaluated before and during treatment with  
385 ELLENCE. Patients with elevated bilirubin or AST may experience slower clearance of  
386 drug with an increase in overall toxicity. Lower doses are recommended in these patients  
387 (see DOSAGE AND ADMINISTRATION). Patients with severe hepatic impairment have  
388 not been evaluated; therefore, epirubicin should not be used in this patient population.

389 **Renal Function.** Serum creatinine should be assessed before and during therapy. Dosage  
390 adjustment is necessary in patients with serum creatinine >5 mg/dL (see DOSAGE AND  
391 ADMINISTRATION). Patients undergoing dialysis have not been studied.

392 **Tumor-Lysis Syndrome.** As with other cytotoxic agents, ELLENCE may induce

393 hyperuricemia as a consequence of the extensive purine catabolism that accompanies drug-  
394 induced rapid lysis of highly chemosensitive neoplastic cells (tumor lysis syndrome).  
395 Other metabolic abnormalities may also occur. While not generally a problem in patients  
396 with breast cancer, physicians should consider the potential for tumor-lysis syndrome in  
397 potentially susceptible patients and should consider monitoring serum uric acid, potassium,  
398 calcium, phosphate, and creatinine immediately after initial chemotherapy administration.  
399 Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia  
400 may minimize potential complications of tumor-lysis syndrome.

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

426 There are no adequate and well-controlled studies in pregnant women. Two pregnancies  
427 have been reported in women taking epirubicin. A 34-year-old woman, 28 weeks pregnant  
428 at her diagnosis of breast cancer, was treated with cyclophosphamide and epirubicin every  
429 3 weeks for 3 cycles. She received the last dose at 34 weeks of pregnancy and delivered a  
430 healthy baby at 35 weeks. A second 34-year-old woman with breast cancer metastatic to  
431 the liver was randomized to FEC-50 but was removed from study because of pregnancy.  
432 She experienced a spontaneous abortion. If epirubicin is used during pregnancy, or if the  
433 patient becomes pregnant while taking this drug, the patient should be apprised of the  
434 potential hazard to the fetus. Women of childbearing potential should be advised to avoid  
435 becoming pregnant.

## 436 **PRECAUTIONS**

### 437 **General**

438 ELLENCE Injection is administered by intravenous infusion. Venous sclerosis may result



439 from an injection into a small vessel or from repeated injections into the same vein.  
440 Extravasation of epirubicin during the infusion may cause local pain, severe tissue lesions  
441 (vesication, severe cellulitis) and necrosis. It is recommended that ELLENCE be slowly  
442 administered into the tubing of a freely running intravenous infusion. Patients receiving  
443 initial therapy at the recommended starting doses of 100-120 mg/m<sup>2</sup> should generally have  
444 epirubicin infused over 15-20 minutes. For patients who require lower epirubicin starting  
445 doses due to organ dysfunction or who require modification of epirubicin doses during  
446 therapy, the epirubicin infusion time may be proportionally decreased, but should not be  
447 less than 3 minutes. (see DOSAGE AND ADMINISTRATION, Preparation of Infusion  
448 Solution). If possible, veins over joints or in extremities with compromised venous or  
449 lymphatic drainage should be avoided. A burning or stinging sensation may be indicative  
450 of perivenous infiltration, and the infusion should be immediately terminated and restarted  
451 in another vein. Perivenous infiltration may occur without causing pain.

452 Facial flushing, as well as local erythematous streaking along the vein, may be indicative  
453 of excessively rapid administration. It may precede local phlebitis or thrombophlebitis.

454 Patients administered the 120-mg/m<sup>2</sup> regimen of ELLENCE as a component of  
455 combination chemotherapy should also receive prophylactic antibiotic therapy with  
456 trimethoprim-sulfamethoxazole (e.g., Septra<sup>®</sup>, Bactrim<sup>®</sup>) or a fluoroquinolone (see  
457 CLINICAL STUDIES, Early Breast Cancer, and DOSAGE AND ADMINISTRATION).

458 Epirubicin is emetogenic. Antiemetics may reduce nausea and vomiting; prophylactic use  
459 of antiemetics should be considered before administration of ELLENCE, particularly when  
460 given in conjunction with other emetogenic drugs.

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

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

#### 466 **Information for Patients**

467 Patients should be informed of the expected adverse effects of epirubicin, including  
468 gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis) and potential  
469 neutropenic complications. Patients should consult their physician if vomiting,  
470 dehydration, fever, evidence of infection, symptoms of CHF, or injection-site pain occurs  
471 following therapy with ELLENCE. Patients should be informed that they will almost  
472 certainly develop alopecia. Patients should be advised that their urine may appear red for 1  
473 to 2 days after administration of ELLENCE and that they should not be alarmed. Patients  
474 should understand that there is a risk of irreversible myocardial damage associated with  
475 treatment with ELLENCE, as well as a risk of treatment-related leukemia. Because  
476 epirubicin may induce chromosomal damage in sperm, men undergoing treatment with  
477 ELLENCE should use effective contraceptive methods. Women treated with ELLENCE  
478 may develop irreversible amenorrhea, or premature menopause.

#### 479 **Laboratory Testing**

480 See WARNINGS. Blood counts, including absolute neutrophil counts, and liver function  
481 should be assessed before and during each cycle of therapy with epirubicin. Repeated  
482 evaluations of LVEF should be performed during therapy.

#### 483 **Drug Interactions**

484 ELLENCE when used in combination with other cytotoxic drugs may show on-treatment

485 additive toxicity, especially hematologic and gastrointestinal effects.

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

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

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

502 Cimetidine increased the AUC of epirubicin by 50%. Cimetidine treatment should be  
503 stopped during treatment with ELLENCE (see CLINICAL PHARMACOLOGY).

#### 504 **Drug-Laboratory Test Interactions**

505 There are no known interactions between ELLENCE and laboratory tests.

#### 506 **Carcinogenesis, Mutagenesis & Impairment of Fertility**

507 See WARNINGS.

#### 508 **Pregnancy**

509 Pregnancy Category D - see WARNINGS.

#### 510 **Nursing Mothers**

511 Epirubicin was excreted into the milk of rats treated with 0.50 mg/kg/day of epirubicin  
512 during peri- and postnatal periods. It is not known whether epirubicin is excreted in human  
513 milk. Because many drugs, including other anthracyclines, are excreted in human milk and  
514 because of the potential for serious adverse reactions in nursing infants from epirubicin,  
515 mothers should discontinue nursing prior to taking this drug.

#### 516 **Geriatric Use**

517 Although a lower starting dose of ELLENCE was not used in trials in elderly female  
518 patients, particular care should be taken in monitoring toxicity when ELLENCE is  
519 administered to female patients  $\geq 70$  years of age. (See CLINICAL PHARMACOLOGY,  
520 Pharmacokinetics in Special Populations.)

#### 521 **Pediatric Use**

522 The safety and effectiveness of epirubicin in pediatric patients have not been established  
523 in adequate and well-controlled clinical trials. Pediatric patients may be at greater risk for  
524 anthracycline-induced acute manifestations of cardiotoxicity and for chronic CHF.

### 525 **ADVERSE REACTIONS**

#### 526 **On-Study Events**

527 Integrated safety data are available from two studies (Studies MA-5 and GFEA-05, see  
528 CLINICAL STUDIES) evaluating epirubicin-containing combination regimens in patients  
529 with early breast cancer. Of the 1260 patients treated in these studies, 620 patients received  
530 the higher-dose epirubicin regimen (FEC-100/CEF-120), 280 patients received the

531 lowerdose epirubicin regimen (FEC-50), and 360 patients received CMF. Serotonin-  
532 specific antiemetic therapy and colonystimulating factors were not used in these trials.  
533 Clinically relevant acute adverse events are summarized in Table 5.

534

535

536 **Table 5. Clinically Relevant Acute Adverse Events in Patients with Early Breast**  
537 **Cancer**  
538

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
<b>Hematologic</b>						
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
<b>Endocrine</b>						
Amenorrhea	71.8	0	69.3	0	67.7	0
Hot flashes	38.9	4.0	5.4	0	69.1	6.4
<b>Body as a Whole</b>						
Lethargy	45.8	1.9	1.1	0	72.7	0.3
Fever	5.2	0	1.4	0	4.5	0
<b>Gastrointestinal</b>						
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
<b>Infection</b>						
Infection	21.5	1.6	15.0	0	25.9	0.6
Febrile neutropenia	NA	6.1	0	0	NA	1.1
<b>Ocular</b>						
Conjunctivitis/keratitis	14.8	0	1.1	0	38.4	0
<b>Skin</b>						
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

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

544 **Delayed Events**

545 Table 6 describes the incidence of delayed adverse events in patients participating in the  
546 MA-5 and GFEA-05 trials.

547 **Table 6. Long-Term Adverse Events in Patients with Early Breast Cancer**

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

548 \*In study MA-5 cardiac function was not monitored after 5 years.

549  
550 Two cases of acute lymphoid leukemia (ALL) were also observed in patients receiving  
551 epirubicin. However, an association between anthracyclines such as epirubicin and ALL  
552 has not been clearly established.

553 **Overview of Acute and Delayed Toxicities**

554 **Hematologic** - See WARNINGS.

555 **Gastrointestinal.** A dose-dependent mucositis (mainly oral stomatitis, less often  
556 esophagitis) may occur in patients treated with epirubicin. Clinical manifestations of  
557 mucositis may include a pain or burning sensation, erythema, erosions, ulcerations,  
558 bleeding, or infections. Mucositis generally appears early after drug administration and, if  
559 severe, may progress over a few days to mucosal ulcerations; most patients recover from  
560 this adverse event by the third week of therapy. Hyperpigmentation of the oral mucosa  
561 may also occur.

562 Nausea, vomiting, and occasionally diarrhea and abdominal pain can also occur. Severe  
563 vomiting and diarrhea may produce dehydration. Antiemetics may reduce nausea and  
564 vomiting; prophylactic use of antiemetics should be considered before therapy (see  
565 PRECAUTIONS).

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

572 **Cardiovascular** - See WARNINGS.

573 **Secondary Leukemia** - See WARNINGS.

574 **Injection-Site Reactions** - See PRECAUTIONS.

575 **OVERDOSAGE**

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

588 If an overdose occurs, supportive treatment (including antibiotic therapy, blood and  
589 platelet transfusions, colonystimulating factors, and intensive care as needed) should be  
590 provided until the recovery of toxicities. Delayed CHF has been observed months after  
591 anthracycline administration. Patients must be observed carefully over time for signs of  
592 CHF and provided with appropriate supportive therapy.

593 **DOSAGE AND ADMINISTRATION**

594 ELLENCE Injection is administered to patients by intravenous infusion. ELLENCE is  
595 given in repeated 3- to 4-week cycles. The total dose of ELLENCE may be given on Day  
596 1 of each cycle or divided equally and given on Days 1 and 8 of each cycle. The  
597 recommended dosages of ELLENCE are as follows:

598 **Starting Doses**

599 The recommended starting dose of ELLENCE is 100 to 120 mg/m<sup>2</sup>. The following  
600 regimens were used in the trials supporting use of ELLENCE as a component of adjuvant  
601 therapy in patients with axillary-node positive breast cancer:

CEF-120:	Cyclophosphamide	75 mg/m <sup>2</sup> PO D 1-14
	ELLENCE	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>
	ELLENCE	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

602

603 Patients administered the 120-mg/m<sup>2</sup> regimen of ELLENCE also received prophylactic  
604 antibiotic therapy with trimethoprim-sulfamethoxazole (e.g., Septra<sup>®</sup>, Bactrim<sup>®</sup>) or a  
605 fluoroquinolone.

606 **Bone Marrow Dysfunction.** Consideration should be given to administration of lower  
607 starting doses (75-90 mg/m<sup>2</sup>) for heavily pretreated patients, patients with pre-existing  
608 bone marrow depression, or in the presence of neoplastic bone marrow infiltration (see  
609 WARNINGS and PRECAUTIONS).

610 **Hepatic Dysfunction.** Definitive recommendations regarding use of ELLENCE in

611 patients with hepatic dysfunction are not available because patients with hepatic  
612 abnormalities were excluded from participation in adjuvant trials of FEC-100/CEF-120  
613 therapy. In patients with elevated serum AST or serum total bilirubin concentrations, the  
614 following dose reductions were recommended in clinical trials, although few patients  
615 experienced hepatic impairment:

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

620 Information regarding experience in patients with hepatic dysfunction is provided in  
621 CLINICAL PHARMACOLOGY, Pharmacokinetics In Special Populations.

622 **Renal Dysfunction.** While no specific dose recommendation can be made based on the  
623 limited available data in patients with renal impairment, lower doses should be  
624 considered in patients with severe renal impairment (serum creatinine > 5 mg/dL).

### 625 **Dose Modifications**

626 Dosage adjustments after the first treatment cycle should be made based on hematologic  
627 and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet  
628 counts <50,000/mm<sup>3</sup>, absolute neutrophil counts (ANC) <250/mm<sup>3</sup>, neutropenic fever, or  
629 Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles  
630 reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in  
631 subsequent courses of treatment should be delayed until platelet counts are ≥100,000/mm<sup>3</sup>,  
632 ANC ≥1500/mm<sup>3</sup>, and nonhematologic toxicities have recovered to ≤ Grade 1.

633 For patients receiving a divided dose of ELLENCE (Day 1 and Day 8), the Day 8 dose  
634 should be 75% of Day 1 if platelet counts are 75,000-100,000/mm<sup>3</sup> and ANC is 1000 to  
635 1499/mm<sup>3</sup>. If Day 8 platelet counts are <75,000/mm<sup>3</sup>, ANC <1000/mm<sup>3</sup>, or Grade 3/4  
636 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

### 637 **Preparation & Administration Precautions**

638 Parenteral drug products should be inspected visually for particulate matter and  
639 discoloration prior to administration, whenever solution and container permit. Procedures  
640 normally used for proper handling and disposal of anticancer drugs should be considered  
641 for use with ELLENCE. Several guidelines on this subject have  
642 been published.<sup>1-8</sup>

643 **Protective measures.** The following protective measures should be taken when handling  
644 ELLENCE:

- 645 • Personnel should be trained in appropriate techniques for reconstitution and handling.
- 646 • Pregnant staff should be excluded from working with this drug.
- 647 • Personnel handling ELLENCE should wear protective clothing: goggles, gowns and  
648 disposable gloves and masks.
- 649 • A designated area should be defined for syringe preparation (preferably under a laminar  
650 flow system), with the work surface protected by disposable, plastic-backed, absorbent  
651 paper.
- 652 • All items used for reconstitution, administration or cleaning (including gloves) should  
653 be placed in high-risk, waste-disposal bags for high temperature incineration.
- 654 Spillage or leakage should be treated with dilute sodium hypochlorite (1% available  
655 chlorine) solution, preferably by soaking, and then water. All contaminated and cleaning  
656 materials should be placed in high-risk, waste-disposal bags for incineration. Accidental

657 contact with the skin or eyes should be treated immediately by copious lavage with water,  
658 or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by  
659 using a scrub brush. Medical attention should be sought. Always wash hands after  
660 removing gloves.

661 **Incompatibilities.** Prolonged contact with any solution of an alkaline pH should be avoided  
662 as it will result in hydrolysis of the drug. ELLENCE should not be mixed with heparin or  
663 fluorouracil due to chemical incompatibility that may lead to precipitation.

664 ELLENCE can be used in combination with other antitumor agents, but it is not  
665 recommended that it be mixed with other drugs in the same syringe.

#### 666 **Preparation of Infusion Solution**

667 ELLENCE is provided as a preservative-free, ready-to-use solution.

668 ELLENCE should be administered into the tubing of a freely flowing intravenous  
669 infusion (0.9% sodium chloride or 5% glucose solution). Patients receiving initial therapy  
670 at the recommended starting doses of 100-120 mg/m<sup>2</sup> should generally have epirubicin  
671 infused over 15-20 minutes. For patients who require lower epirubicin starting doses due to  
672 organ dysfunction or who require modification of epirubicin doses during therapy, the  
673 epirubicin infusion time may be proportionally decreased, but should not be less than 3  
674 minutes. This technique is intended to minimize the risk of thrombosis or perivenous  
675 extravasation, which could lead to severe cellulitis, vesication, or tissue necrosis. A direct  
676 push injection is not recommended due to the risk of extravasation, which may occur even  
677 in the presence of adequate blood return upon needle aspiration. Venous sclerosis may  
678 result from injection into small vessels or repeated injections into the same vein (see  
679 PRECAUTIONS). ELLENCE should be used within 24 hours of first penetration of the  
680 rubber stopper. Discard any unused solution.

#### 681 **HOW SUPPLIED**

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

685 50 mg/25 mL single-use vial NDC 0009-5091-01

686 200 mg/100 mL single-use vial NDC 0009-5093-01

687 Store refrigerated between 2°C and 8°C (36°F and 46°F). Do not freeze. Protect from light.

688 Discard unused portion.

#### 689 **Rx only**

690 US Patent No. 5,977,082

691 Manufactured for: Pharmacia & Upjohn Company, A subsidiary of Pharmacia Corporation,  
692 Kalamazoo, MI 49001 USA

693 By: Pharmacia (Perth) Pty Limited, Bentley WA 6102 Australia

694 February 2005

TBDTBD

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