For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Epirubicin Hydrochloride Injection

ANTHRACIN

WARNING

- Epirubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
- Severe local tissue necrosis will occur if there is extravasation during administration.
- Epirubicin must not be given by the intramuscular or subcutaneous route.
- Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with epirubicin or months to years after termination of therapy.
- Cardiac toxicity with Epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.
- Secondary acute myelogenous leukemia (AML) has been reported in patients with breast cancer treated with anthracyclines, including epirubicin. The occurrence of refractory secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated.
- Dosage should be reduced in patients with impaired hepatic function
- Severe myelosuppression may occur.

DESCRIPTION:

ANTHRACIN (Epirubicin Hydrochloride) is an anthracycline cytotoxic antibiotic structurally related to doxorubicin. It is among the most active single agents used in the management of breast cancer and has shown activity in a variety of cancers including soft-tissue sarcomas, ovarian and lung cancers. It has a molecular formula of $C_{27}H_{29}NO_{11}$.HCl and molecular weight of 579.95.

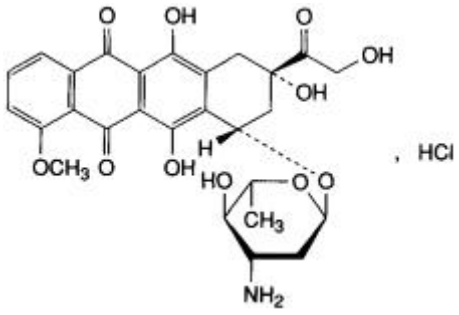
COMPOSITION:

Each ml contains:

Epirubicin Hydrochloride BP	2.0 mg
Sodium Chloride BP	9.0 mg
Water for Injections BP	q.s
Also contains Hydrochloric Acid BP	to adjust pH

CHEMICAL STRUCTURE:

Epirubicin (4' - epidoxorubicin) is the 4'-epimer of doxorubicin. It is chemically (8S- ***cis***)-10-[(3-amino-2, 3,6-trideoxy-14 α-L- *arabino*-hexopyranosyl) oxy]-7,8,9,10- tetrahydro-6, 8,11-trihydroxy-8-15 (hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride. The structural formula of epirubicin is as below:



PHARMACOLOGY:
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.

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 epirubicin at doses of 60 to 150 mg/m2 in patients with solid tumors are shown in Table 1. The plasma concentration declined in a triphasic manner with mean half-lives for the alpha, beta, and gamma phases of about 3 minutes, 2.5 hours, and 33 hours, respectively.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters in Patients [1] with Solid Tumors Receiving Intravenous Epirubicin 60 to 150 mg/m²

Dose [2] (mg/m²)	Cmax[3] (µg/mL)	(µg•h/mL) AUC [4]	t ½[5] (hours)	CL[6] (L/hour)	Vss[7] (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

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

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

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

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

Gender:
In patient's ≤ 50 years of age, mean clearance values in adult male and female patients were similar. The clearance of epirubicin is decreased in elderly women.

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

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

Hepatic Impairment
Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups. Patients in Group 1 (n=22) had serum AST (SGOT) levels above the upper limit of normal (median: 93 IU/L) and normal serum bilirubin levels (median: 0.5 mg/dL) and were given epirubicin doses of 12.5 to 90 mg/m². Patients in Group 2 had alterations in both serum AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an epirubicin dose of 25 mg/m² (n=8). Their pharmacokinetics was compared to those of patients with normal serum AST and bilirubin values, who received epirubicin doses of 12.5 to 120 mg/m². The median plasma clearance of epirubicin was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated.

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 Patients on dialysis have not been studied.

CLINICAL STUDIES:
Two randomized, open-label, multicenter studies evaluated the use of ANTHRACIN Injection 100 to 120 mg/m² in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m² of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized premenopausal and perimenopausal women with one or more positive lymph nodes to an epirubicin-containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m² of epirubicin 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 2 shows the treatment regimens that the patients received. The primary endpoint of the trials was relapse-free survival, ie, time to occurrence of a local, regional, or distant recurrence, or disease-related death. Patients with contralateral breast cancer, second primary malignancy or death from causes other than breast cancer were censored at the time of the last visit prior to these events.

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

	Treatment Groups	Agent	Regimen
MA-5[1] N=716	CEF-120 (total, 6 cycles)[2] N=356	Cyclophosphamide	75 mg/m² PO, d 1-14, q 28 days
		ANTHRACIN	60 mg/m² IV, d 1 & 8, q 28 days
		Fluorouracil	500 mg/m² IV, d 1 & 8, q 28 days

	CMF (total, 6 cycles) N=360	Cyclophosphamide	100 mg/m² PO, d 1-14, q 28 days
		Methotrexate	40 mg/m² IV, d 1 & 8, q 28 days
		Fluorouracil	600 mg/m² IV, d 1 & 8, q 28 days
GFEA-05[3] N=565	FEC-100 (total, 6 cycles) N=276	Fluorouracil	500 mg/m² IV, d 1, q 21 days
		ANTHRACIN	100 mg/m² IV, d 1, q 21 days
		Cyclophosphamide	500 mg/m² IV, d 1, q 21 days
	FEC-50 (total, 6 cycles) N=289 Tamoxifen 30 mg daily x 3 years, postmenopausal women, any receptor status	Fluorouracil	500 mg/m² IV, d 1, q 21 days
		ANTHRACIN	50 mg/m² IV, d 1, q 21 days
		Cyclophosphamide	500 mg/m² IV, d 1, q 21 days

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

In the MA-5 trial, the median age of the study population was 45 years. Approximately 60% of patients had 1 to 3 involved nodes and approximately 40% had 4 nodes involved with tumor. In the GFEA-05 study, the median age was 51 years and approximately half of the patients were postmenopausal. About 17% of the study population had 1 to 3 positive nodes and 80% of patients had 4 involved lymph nodes. Demographic and tumor characteristics were well-balanced between treatment arms in each study.

The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results 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.

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 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 3.

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 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
RFS at 5 yrs (%)	62	53	65	52
Hazard ratio†	0.76		0.68	
2-sided 95% CI	(0.60, 0.96)		(0.52, 0.89)	
Log-rank Test stratified**	(p = 0.013)		(p = 0.007)	
OS at 5 yrs (%)	77	70	76	65
Hazard ratio†	0.71		0.69	
2-sided 95% CI	(0.52, 0.98)		(0.51, 0.92)	
Log-rank Test stratified**	(p = 0.043) (unstratified p= 0.13)		(p = 0.007)	
RFS at 10 yrs (%)	51	44	49	43
Hazard ratio†	0.78		0.78	
2-sided 95% CI	(0.63, 0.95)		(0.62, 0.99)	
Log-rank Test stratified**	(p = 0.017) (unstratified p= 0.023)		(p = 0.040) (unstratified p = 0.09)	
OS at 10 yrs (%)	61	57	56	50
Hazard ratio†	0.82		0.75	
2-sided 95% CI	(0.65, 1.04)		(0.58, 0.96)	
Log-rank Test stratified**	(p = 0.100) (unstratified p= 0.18)		(p = 0.023) (unstratified p= 0.039)	

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

INDICATIONS:
Epirubicin is used as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.

CONTRAINDICATIONS:

Patients should not be treated with Epirubicin Injection if they have any of the following conditions: baseline neutrophil count < 1500 cells/mm3; severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias; previous treatment with anthracyclines up to the maximum cumulative dose; hypersensitivity to epirubicin, other anthracyclines, or anthracenediones; or severe hepatic dysfunction.

ADVERSE EFFECTS:

On-Study Events

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

Table 5: 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	71.8	0	69.3	0	67.7	0
Amenorrhea 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 + epirubicin + 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 6 describes the incidence of delayed adverse events in patients participating in the MA-5 and GFEA-05 trials.

Table 6: Long-Term Adverse Events in Patients with Early Breast Cancer

	% of Patients		
Event	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 epirubicin. However, an association between anthracyclines such as epirubicin and ALL has not been clearly established.

Hematologic:

A dose-dependent, reversible leukopenia and/or neutropenia is the predominant manifestation of hematologic toxicity associated with epirubicin 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, ANTHRACIN at the recommended dose in combination with cyclophosphamide and fluorouracil can produce severe leukopenia and neutropenia. Severe thrombocytopenia and anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, septicemia, septic shock, hemorrhage, tissue hypoxia, symptomatic anemia, or death. If myelosuppressive complications occur, appropriate supportive measures (e.g., intravenous antibiotics, colony-stimulating factors, transfusions) may be required. Myelosuppression requires careful monitoring. Total and differential WBC, red blood cell (RBC), and platelet counts should be assessed before and during each cycle of therapy with ANTHRACIN.

Gastrointestinal:

A dose-dependent mucositis (mainly oral stomatitis, less often esophagitis) may occur in patients treated with epirubicin. 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; prophylactic use of antiemetics should be considered before therapy.

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 epirubicin; signs and symptoms of these reactions may vary from skin rash and pruritus to fever, chills, and shock.

Cardiovascular:

Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. Early cardiac toxicity of epirubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of epirubicin 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 ANTHRACIN and represents the cumulative dose-limiting toxicity of the drug. If it occurs, delayed cardiotoxicity usually develops late in the course of therapy with ANTHRACIN or within 2 to 3 months after completion of treatment, but later events (several months to years after treatment termination) have been reported.

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 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 cumulative probability of developing AML/MDS was found to be particularly increased in patients who received more than the maximum recommended cumulative dose of epirubicin (720 mg/m²) or cyclophosphamide (6,300 mg/m²), as shown in Table 4.

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

Years from Treatment Start	Cumulative Probability of Developing AML/MDS % (95% CI)			
	Cyclophosphamide Cumulative Dose ≤ 6,300 mg/m²		Cyclophosphamide Cumulative Dose > 6,300 mg/m²	
	Epirubicin Cumulative Dose ≤ 720 mg/m² N=4760	Epirubicin Cumulative Dose > 720 mg/m² N=111	Epirubicin Cumulative Dose ≤ 720 mg/m² N=890	Epirubicin Cumulative Dose > 720 mg/m² 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:

Extravasation of epirubicin during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. It is recommended that ANTHRACIN be slowly administered into the tubing of a freely running intravenous infusion.

DRUG INTERACTIONS:

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

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

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

Taxane: The administration of epirubicin (90 mg/m²) immediately prior to paclitaxel (175 mg/m²) or docetaxel (70 to 80 mg/m²) did not affect the pharmacokinetics of epirubicin but did result in increases in systemic exposure to epirubicin's inactive metabolites epirubicinol and 7-deoxy doxorubicin aglycone. When paclitaxel (175 mg/m²) was administered prior to epirubicin (90 mg/m²) an increase in the AUCs of epirubicin, epirubicinol and 7-deoxy doxorubicin aglycone was seen.

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

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.

PRECAUTIONS:
General

ANTHRACIN Injection is administered by intravenous infusion. Venous sclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Extravasation of epirubicin during the infusion may cause local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. It is recommended that ANTHRACIN be slowly administered into the tubing of a freely running intravenous infusion. Patients receiving initial therapy at the recommended starting doses of 100-120 mg/m² should generally have epirubicin infused over 15-20 minutes. For patients who require lower epirubicin starting doses due to organ dysfunction or who require modification of epirubicin doses during therapy, the epirubicin infusion time may be proportionally decreased, but should not be less than 3 minutes. If possible, veins over joints or in extremities with compromised venous or lymphatic drainage should be avoided. A burning or stinging sensation may be indicative of perivenous infiltration, and the infusion should be immediately terminated and restarted in another vein. 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.

Patients administered the 120-mg/m² regimen of ANTHRACIN as a component of combination chemotherapy should also receive prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole or a fluoroquinolone

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

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

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

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 epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from epirubicin, mothers should discontinue nursing prior to taking this drug.

Geriatric Use

Although a lower starting dose of ANTHRACIN was not used in trials in elderly female patients, particular care should be taken in monitoring toxicity when ANTHRACIN is administered to female patients ≥ 70 years of age.

Pediatric Use

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

WARNINGS:

ANTHRACIN Injection should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Before beginning treatment with epirubicin, patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment. Also, initial treatment with ANTHRACIN should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left ventricular ejection function (LVEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression. Supportive care may be necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to epirubicin.

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.

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

Use in pregnancy and lactation:
Pregnancy category: D

ANTHRACIN may 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 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 epirubicin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

DOSAGE:

ANTHRACIN Injection is intended for intravenous administration only. ANTHRACIN is to be given in repeated 3-4 week cycles .The total dose may be given on day 1 of each cycle or may be divided equally and given on days1 and 8 of each cycle. The recommended dosages of ANTHRACIN are as follows:

Starting Doses

The recommended starting dose of ANTHRACIN is 100 to 120 mg/m². The following regimens were used in the trials supporting use of ANTHRACIN as a component of adjuvant therapy in patients with axillary-node positive breast cancer:

CEF-120:	Cyclophosphamide	75 mg/m² PO D 1-14
	ANTHRACIN	60 mg/m² IV D 1, 8
	5-Fluorouracil	500 mg/m² IV D 1, 8
	Repeated every 28 days for 6 cycles	
FEC-100:	5-Fluorouracil	500 mg/m²
	ANTHRACIN	100 mg/m²
	Cyclophosphamide	500 mg/m²

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

Bone Marrow Dysfunction: Consideration should be given to administration of lower starting doses (75-90 mg/m²) for heavily pretreated patients, patients with pre-existing bone marrow depression, or in the presence of neoplastic bone marrow infiltration.

Hepatic Dysfunction: Definitive recommendations regarding use of ANTHRACIN in patients with hepatic dysfunction are not available because patients with hepatic abnormalities were excluded from participation in adjuvant trials of FEC-100/CEF-120 therapy. In patients with elevated serum AST or serum total bilirubin concentrations, the following dose reductions were recommended in clinical trials, although few patients experienced hepatic impairment:

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

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

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

Dose Modifications

Dosage adjustments after the first treatment cycle should be made based on hematologic and nonhematologic toxicities. Patients experiencing during treatment cycle nadir platelet counts < 50,000/mm³, absolute neutrophil counts (ANC) < 250/mm³, neutropenic fever, or Grades 3/4 nonhematologic toxicity should have the Day 1 dose in subsequent cycles reduced to 75% of the Day 1 dose given in the current cycle. Day 1 chemotherapy in subsequent courses of treatment should be delayed until platelet counts are ≥ 100,000/mm³, ANC ≥ 1500/mm³, and nonhematologic toxicities have recovered to Grade ≤ 1.

For patients receiving a divided dose of ANTHRACIN (Day 1 and Day 8), the Day 8 dose should be 75% of Day 1 if platelet counts are 75,000-100,000/mm³ and ANC is 1000 to 1499/mm³. If Day 8 platelet counts are < 75,000/mm³, ANC < 1000/mm³, or Grade 3/4 nonhematologic toxicity has occurred, the Day 8 dose should be omitted.

ADMINISTRATION:

- Epirubicin is administered intravenously by slow injection or continuous infusion.
- Allow vials to reach to room temperature before using them.
- It is recommended that epirubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Glucose Injection USP. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. The dosage should be administered in not less than 3 to 4 minutes. 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. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.
- Extravasation during I.V. administration may results in significant local damage and ulceration. The integrity of the vein must be assured, with the needle remaining in place throughout epirubicin administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein.
- When used in combination with other chemotherapeutic antineoplastic agents, drugs must not be mixed in the same syringe.
- Epirubicin injection should not be mixed with heparin due to chemical incompatibility, which may lead to precipitation.

Overdosage:

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

HANDLING AND DISPOSAL:
Use of 5 % sodium hypochlorite solution is recommended as neutralizing agent in cases of spills or leak of this solution.

STORAGE:
Store under refrigeration at 2 - 8^{o}C (36 – 46°F). Do not freeze. Protect from light.

PRESENTATION:
ANTHRACIN is available as 5 ml and 25 ml injection containing 10 mg and 50 mg of Epirubicin Hydrochloride, respectively.

Mfd. in India by:
Fresenius Kabi Oncology Ltd.
Village Kishanpura
P.O Guru Majra
Tehsil-Nalagarh
Distt. Solan (H.P)- 174101

REFERENCES:
1. Prescribing Information, Ellence®; Pharmacia (Perth) Pty Limited, Bentley WA 6102 Australia,March 2, 2005

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