Lactation
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 reaction in nursing infants from epirubicin, mothers should discontinue nursing prior to taking this drug.

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.

Geriatric Use
Although a lower starting dose of epirubicin was not used in trials in elderly female patients, particular care should be taken in monitoring toxicity when epirubicin is administered to female patients>/=70 years of age.

Undesirable effects:
Epirubicin should only be administered under the supervision of qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin. Extravasation of epirubicin from the vein during injection may cause severe tissue lesion and necrosis. Venous sclerosis may result from injection into small vessles or repeated injection into the same vein. Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin. During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules, reaching a nadir between the 10^{th} and 14^{th} day values should return to normal by the 21^{st} day; they are more severe with high dose schedules. Thrombocytopenia (<100,000 platelets/mm^3) is experienced in very few patients even following high doses of epirubicin. In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900-1000 mg/m^2 should only be exceeded with extreem caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increase greatly. An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as Flattering or inversion of T-wave, depression of the S-T segment, the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses<900 mg/m^2, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac functions by non-invasive tecniques such as ECG, echocardiography and, if necessary measurement of ejection fraction by radionuclide angiography. Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase the patient who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area. Before commencing therapy with epirubicin, and if possible during treatment liver function should be evaluated (SGOT, SGT, alkanine phosphatase, billirubin). As with other cytotoxic agents, epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that this phenomenon may be recognised and properly managed.
Epirubicin may impart a red colour to the urine for one or two days after administration.

OVERDOSE
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 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.

STORAGE
Store between 15°C - 30°C. Protect from light. Store reconstituted solution at 2-8°C(36°F-46°F)

PRESENTATION
Epiruba -10 mg and 50 mg is available as a sterile lyophilized powder for injection in a 10 ml and 30 ml clear glass vial

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700EHDM0915-00

GETWELL

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

Epirubicin Hydrochloride for Injection

EPIRUBA™

LYOPHILIZED

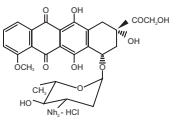
FOR I.V INFUSION ONLY

Rx only

WARNING

1. Severe local tissue necrosis will occur if there is extravasation during administration. 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^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution. Active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity. Cardiac toxicity with Epirubicin 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.
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.

DESCRIPTION
EPIRUBA™ (Epirubicin Hydrochloride for Injection) is a new anthracycline cytotoxic antibiotic with antiblastic activity. Its structural formula is as follows:



COMPOSITION

EPIRUBA™ -10 mg

Each vial contains	
Epirubicin Hydrochloride BP	10 mg
Lactose Monohydrate IP	50 mg

EPIRUBA™ -50 mg

Each vial contains	
Epirubicin Hydrochloride BP	50 mg
Lactose Monohydrate IP	250 mg

Pharmacology

Pharmacodynamics:
Epirubicin is an anthracycline cytotoxic agent. Although it is known that anthracyclines can interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of epirubicin's cytotoxic and/or antiproliferative properties have not been completely elucidated. Epirubicin forms a complex with DNA by intercalation of its planar rings between nucleotide base pairs, with consequent inhibition of nucleic acid (DNA and RNA) and protein synthesis. Such intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Epirubicin also inhibits DNA helicase activity, preventing the enzymatic separation of double-stranded DNA and interfering with replication and transcription. Epirubicin is also involved in oxidation/reduction reactions by generating cytotoxic free radicals. The antiproliferative and cytotoxic activity of epirubicin is thought to result from these or other possible mechanisms. Epirubicin is cytotoxic in vitro to a variety of established murine and human cell lines and primary cultures of human tumors. It is also active in vivo against a variety of murine tumors and human xenografts in athymic mice, including breast tumors.

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/m^2 in patients with solid tumors are shown in below table . 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 - Summary of Mean (±SD) Pharmacokinetic Parameters in Patients 1 with Solid Tumors Receiving Intravenous Epirubicin 60 to 150 mg/m^2

Dose[2] (mg/m^2)	C_{max}[3] (µg/mL)	(µgh/mL) auc[4]	T½[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 concentrations are approximately twice those of plasma.

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

1. Reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative, epirubicinol;
2. conjugation of both the unchanged drug and epirubicinol with glucuronic acid;
3. loss of the amino sugar moiety through a hydrolytic process with the formation of the doxorubicin and doxorubicinol aglycones; and
4. loss of the amino sugar moiety through a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-doxorubicinol aglycone. Epirubicinol has in vitro cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug, they are unlikely to reach in vivo concentrations sufficient for cytotoxicity. No signi-ficant 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 patients ≤50 years of age, mean clearance values in adult male and female patients were similar. The clearance of epirubicin is decreased in elderly women.

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

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

Hepatic Impairment- Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups. Patients 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 were 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.

INDICATIONS(S)

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

DOSAGE & ADMINISTRATION

Epirubicin Injection is administered to patients by intravenous infusion. Epirubicin is given in repeated 3- to 4-week cycles. The total dose of Epirubicin may be given on day 1 of each cycle or divided equally and given on days 1 and 8 of each cycle. The recommended dosages of Epirubicin are as follows:

Starting Doses

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

CEF-120:	Cyclophosphamide	75 mg/m² PO d 1-14
	Epirubicin	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
	Epirubicin	100 mg/m²
	Cyclophosphamide	500 mg/m²
	All drugs administered intravenously on day 1 and repeated 21 day for cycles	

Patients administered the 120 mg/m² regimen of Epirubicin also received prophylactic antibiotic therapy with trimethoprimsulfamethoxazole or a fluoroquinolone.

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 Epirubicin 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 epirubicin (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.

Preparation & administration precautions

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Procedures normally used for proper handling and disposal of anticancer drugs should be considered for use with epirubicin. Several guidelines on this subject have been published.

Protective measures- The following protective measures should be taken when handling epirubicin:

Personnel should be trained in appropriate techniques for reconstitution and handling.

Pregnant staff should be excluded from working with this drug.

Personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.

A designated area should be defined for syringe preparation (preferably under a laminar flow system), with the work surface protected by disposable, plastic-backed, absorbent paper.

All items used for reconstitution, administration or cleaning (including gloves) should be placed in high-risk, waste-disposal bags for high temperature incineration.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All contaminated and cleaning materials should be placed in high-risk, waste-disposal bags for incineration. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Medical attention should be sought. Always wash hands after removing gloves.

Incompatibilities. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Epirubicin should not be mixed with heparin or fluorouracil due to chemical incompatibility that may lead to precipitation. Epirubicin can be used in combination with other antitumor agents, but it is not recommended that it be mixed with other drugs in the same syringe.

Preparation of infusion solution

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

Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (o.9% sodium chloride or 5% glucose solution). 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. This technique is intended to minimize the risk of thrombosis or perivenous extravasation, which could lead to severe cellulitis, vesication, or tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. Epirubicin should be used within 24 hours of first penetration of the rubber stopper . Discard any unused solution.

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

Drug Interactions:

Epirubicin when used in combination with other cytotoxic drugs may show on-treatment additive toxicity, especially hematologic and gastrointestinal effects. Concomitant use of epirubicin 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 concomitanily 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 epirubicin after previous radiation therapy may induce an inflammatory recall reaction at the site of the irradiation. Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may effect epirubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity. Cimetidine increased the AUC of epirubicin by 50% Cimetidine treatment should be stopped during treatment with epirubicin.

Drug-laboratory test interactions

There are no known interactions between epirubicin and laboratory tests.

Laboratory Testing

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

Pregnancy:

There are no adequate and well-controlled studies in pregnant woman.