PRODUCT MONOGRAPH

PrEPIRUBICIN HYDROCHLORIDE INJECTION

2 mg/mL

Sterile Solution for Intravenous use

Antineoplastic agent

Strides Pharma Canada Inc.
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PrEPIRUBICIN HYDROCHLORIDE INJECTION

PART I: HEALTH PROFESSIONAL INFORMATION

CAUTION

EPIRUBICIN HYDROCHLORIDE INJECTION IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. IRREVERSIBLE CARDIAC TOXICITY MAY OCCUR AS THE CUMULATIVE DOSE APPROACHES 1000 mg/m^2. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR RECEIVED PRIOR EPIRUBICIN CUMULATIVE DOSES EXCEEDING 650 mg/m^2.

SECONDARY ACUTE MYELOID LEUKEMIA (AML) WITH OR WITHOUT A PRELEUKEMIC PHASE (MYELODYSPLASTIC SYNDROME OR MDS) HAS BEEN REPORTED IN PATIENTS TREATED WITH EPIRUBICIN-CONTAINING REGIMENS. THE CUMULATIVE RISK OF DEVELOPING TREATMENT-RELATED AML/MDS IN 7110 PATIENTS WITH EARLY 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.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Sterile solution for injection / 2 mg/mL	Hydrochloric acid, Sodium chloride and water for injection

INDICATIONS AND CLINICAL USE

Epirubicin Hydrochloride Injection has been used successfully as a single agent and in combination with other chemotherapeutic agents to produce regression in a variety of tumour types such as lymphoma, lung, cancer of the breast, ovary and stomach.

Epirubicin Hydrochloride Injection is recommended for the treatment of metastatic breast cancer.

Epirubicin Hydrochloride Injection may also be used as a component in the adjuvant treatment of early stage breast cancer for pre- and peri- menopausal women.

Epirubicin Hydrochloride Injection is also recommended in small cell lung cancer (both limited and extensive disease) advanced non-small cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, Stage III and IV (FIGO) ovarian carcinoma and metastatic and locally unresectable gastric carcinoma.

CONTRAINDICATIONS

- Hypersensitivity to epirubicin or any other component of the product, or other anthracyclines or anthracenediones such as doxorubicin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- marked persistent myelosuppression induced by prior treatment with other antitumour agents or by radiotherapy
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- history of severe cardiac disease
- previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- EPIRUBICIN HYDROCHLORIDE INJECTION IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. IRREVERSIBLE CARDIAC TOXICITY MAY OCCUR AS THE CUMULATIVE DOSE APPROACHES 1000 mg/m^2. CARDIAC MONITORING IS ADVISED IN THOSE PATIENTS WHO HAVE RECEIVED MEDIASTINAL RADIOTHERAPY, OTHER ANTHRACYCLINE OR ANTHRACENE THERAPY, WITH PRE-EXISTING CARDIAC DISEASE, OR RECEIVED PRIOR EPIRUBICIN CUMULATIVE DOSES EXCEEDING 650 mg/m^2.

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- SEVERE LOCAL TISSUE NECROSIS ASSOCIATED WITH EXTRAVASATION DURING ADMINISTRATION

- MYOCARDIA TOXICITY, MANIFESTED IN ITS MOST SEVERE FORM BY POTENTIALLY FATAL CONGESTIVE HEART FAILURE (CHF)

- SEVERE MYELOSUPRESSION

Cardiac Function:

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and 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 a consideration for the discontinuation of epirubicin treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events several months to years after completion of treatment have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary edema, dependent edema,

cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of Epirubicin Hydrochloride Injection therapy.

Given the risk of cardiomyopathy, a cumulative dose of 900 to 1000 mg/m^2 epirubicin should generally not be exceeded. Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs. Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored.

Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The reported half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. While cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present, it may be more likely to occur at lower cumulative doses in patients with these risk factors.

Available evidence appears to indicate that cardiotoxicity is cumulative across members of the anthracycline and anthracene class of drugs. Patients who have previously received other anthracyclines and anthracenes are at particular risk for possible cardiotoxic effects of Epirubicin Hydrochloride Injection at a lower total dose than previously untreated patients and, therefore, should be carefully monitored. The total dose of Epirubicin Hydrochloride Injection administered to a patient should take into account: prior or concomitant therapy with related compounds such as doxorubicin and daunorubicin or anthracene derivatives; and/or radiotherapy to the mediastinal

area.

Anthracycline-induced cardiac failure is often resistant to currently available therapeutic and physical measures used for the treatment of cardiac failure. Early clinical diagnosis of drug-induced heart failure is essential. Treatment measures include digitalis, diuretics, peripheral vasodilators, low salt diet, and bed rest. Severe cardiac toxicity may occur precipitously without antecedent EKG changes. An EKG, echocardiogram or radionuclide angiography (MUGA) performed at baseline and prior to each dose or course after a cumulative dose of 650 mg/m^2 is suggested. Transient EKG changes consisting of T-wave flattening, S-T depression and arrhythmias occurring up to two weeks after a dose or course of Epirubicin Hydrochloride Injection are presently not considered indications for suspension of Epirubicin Hydrochloride Injection therapy.

Epirubicin cardiomyopathy has been reported to be associated with a reduction of the ejection fraction as determined by radionuclide scan or echocardiography. None of these tests have yet consistently identified those individual patients that are approaching their maximally tolerated cumulative dose of epirubicin. If test results indicate a change in cardiac status associated with Epirubicin Hydrochloride Injection therapy, the benefit of continued therapy must be carefully weighed against the risk of producing irreversible cardiac damage.

Hematologic Toxicity:

Careful hematologic monitoring is required since bone marrow depression, primarily of leukocytes may occur. Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell counts (WBC).

With the recommended dosage schedule (see DOSAGE AND ADMINISTRATION) leukopenia is transient, reaching its nadir 10-14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as $1000/mm^3$ are to be expected during treatment with Epirubicin Hydrochloride Injection.

Red blood cell and platelet levels should be monitored since they may also be depressed. Haematologic toxicity may require dose reduction or delay or suspension of Epirubicin Hydrochloride Injection therapy. Persistent myelosuppression may result in infection or haemorrhage.

Epirubicin may potentiate the toxicity of other anticancer therapies as well as radiation induced toxicity to the myocardium, mucosa and skin. Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia and generalized infections) of prior cytotoxic treatment before beginning treatment with Epirubicin Hydrochloride Injection.

While treatment with high doses of epirubicin (e.g., ≥ 90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of the drug does require special attention for possible clinical complications due to profound myelosuppression.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including epirubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Liver Function:

Epirubicin is extensively metabolized by the liver and its major route of elimination is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see DOSAGE AND ADMINISTRATION). Patients with severe hepatic impairment should not receive epirubicin (see CONTRAINDICATIONS).

Renal Function:

Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine > 5 mg/dL (see DOSAGE AND ADMINISTRATION).

Secondary Leukemia:

The occurrence of secondary acute myeloid leukemia (AML) with or without a preleukemic phase (myelodysplastic syndrome or MDS) has been reported in patients treated with epirubicin-containing regimens. Such cases could have a short (1-3 years) latency period (see below and in Table 2 under ADVERSE REACTIONS).

The quantified risk of developing acute myeloid leukemia (AML), including myelodysplastic syndrome (MDS), following epirubicin or epirubicin-containing therapy, has been estimated by analyzing data collected prospectively from 19 randomized trials for the adjuvant treatment of early breast cancer, that were either company-sponsored or conducted by independent institutions (including the National Institute of Canada's MA.5 trial, see CLINICAL TRIALS, Early Stage Breast Cancer Studies). As of 31 December 2001, 28 (0.39%) of the 7,110 evaluable patients treated with epirubicin, had presented with either AML or MDS. An additional 4 patients were diagnosed with other types of leukemia: 3 with acute lymphoblastic leukemia (ALL), and 1 with chronic lymphocytic leukemia (CLL). The time elapsed from the start of adjuvant treatment to the diagnosis of AML/MDS ranged from 8 to 126 months, with a median

of 33 months. Of the 23 cases of AML/MDS for whom cytogenetic information was available, in 12 there was evidence of balanced chromosome translocations, and in 7 these translocations involved chromosome 11 or 21. Therapy-induced leukemia secondary to topoisomerase inhibitors generally has a short induction period (6 months to 5 years) and is known to be associated with translocations involving chromosome 11 or 21.

In this most recent analysis, the cumulative risk of developing AML/MDS in the 7,110 patients treated with epirubicin was 0.27% (95% confidence interval 0.14%, 0.40%) at 3 years, 0.46% (95% confidence interval 0.28%, 0.65%) at 5 years, and 0.55% (95% confidence interval, 0.33%, 0.78%) at 8 years. AML/MDS rates increased with epirubicin dose per cycle, and cumulative dose. For instance, in the MA.5 trial, in patients that received intensive doses of epirubicin (120 mg/m^2), the incidence of AML/MDS was 1.1% at 5 years with no additional cases observed during the second 5 years (years 6-10) of follow-up.

Since the completion of these analyses, in the period up to and including September 2003, further spontaneous, literature and study reports of AML/MDS have been received.

In addition, in 10 trials for the treatment of advanced breast cancer (3061 patients, follow-up until March 1999), two cases of AML occurred. However, due to the small number of cases and the limited follow-up as a result of the natural history of advanced breast cancer in these patients, risk estimates could not be made for this patient population.

General:

Epirubicin Hydrochloride Injection must not be administered by intramuscular or subcutaneous injection.

Severe local tissue necrosis can occur if Epirubicin Hydrochloride Injection is extravasated during intravenous administration. Extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle (see DOSAGE AND ADMINISTRATION). If signs or symptoms of extravasation occur the injection or infusion should be terminated immediately and restarted in another vein.

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.

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals and has been associated with an increased risk of secondary leukemia (AML) in clinical trials of adjuvant treatment of breast cancer (see ADVERSE REACTIONS). In addition, epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Epirubicin imparts a red colouration to the urine for 1 or 2 days after administration. Patients should be advised to expect this during active therapy.

Usage in Pregnancy:

There is no conclusive information about epirubicin adversely affecting human fertility, or causing teratogenesis; however, at high doses epirubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no studies in pregnant women. Therefore, women of childbearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods.

Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If Epirubicin Hydrochloride Injection is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be informed of the potential hazard to the fetus. Mothers should be advised not to breast-feed while undergoing chemotherapy with Epirubicin Hydrochloride Injection.

Monitoring and Laboratory Tests:

Initial treatment with Epirubicin Hydrochloride Injection requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, Epirubicin Hydrochloride Injection may induce hyperuricemia secondary to rapid lysis of neoplastic cells. The physician should monitor the patient's serum chemistry and blood uric acid level and be prepared to institute appropriate measures that might be necessary to control this problem. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Epirubicin Hydrochloride Injection is not an anti-microbial agent.

Information to be given to the patient:

Patients should be counseled about the known adverse effects that they could experience during chemotherapy with Epirubicin Hydrochloride Injection, including cardiotoxicity, myelosuppression and risk of infection, thrombocytopenia, anemia, nausea, vomiting, and stomatitis.

Physicians should also clearly lay out early on the risks and benefits of the various chemotherapeutic options available, thus enabling the patient to make an informed treatment choice. Patients should be aware that higher dose regimens may have a greater toxicity that includes secondary leukemia. Wherever possible, the physician should discuss the information presented in the 'CONSUMER INFORMATION' section.

ADVERSE REACTIONS

Dose limiting toxicities are myelosuppression and cardiotoxicity (see WARNINGS AND PRECAUTIONS). Other reactions reported are:

Cutaneous - Reversible partial or complete alopecia occurs in most patients. Alopecia and lack of beard growth in males are usually reversible. Recall of skin reaction associated with prior radiotherapy may occur with epirubicin administration. Local toxicity, rash/itch and skin changes may also occur.

Gastrointestinal - Acute nausea and vomiting occurs frequently in most patients. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) has been reported to occur 5-10 days after administration. This may lead to ulceration and represents a site of origin for severe infections. Diarrhea has been reported. Most patients recover from this adverse event by the third week of therapy.

Local - Severe cellulitis, vesication, local pain and tissue necrosis can occur if epirubicin is extravasated during administration (see DOSAGE AND ADMINISTRATION). Erythematous streaking and/or transient urticaria along the vein proximal to the site of administration may occur. Venous sclerosis may result from injection into small veins or repeated injection into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see SPECIAL HANDLING INSTRUCTIONS).

Haematological - A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) are the predominant manifestations of epirubicin bone marrow/haematologic toxicity and represents the acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are usually more severe after administration of high-dose regimens; under these conditions appropriate bone marrow support (eg. peripheral blood progenitor cells and/or colony- stimulating factors) may be required. Thrombocytopenia, anemia, pancytopenia, neutropenia and febrile neutropenia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia: see WARNINGS AND PRECAUTIONS.

Body as a Whole - Phlebitis, thromboembolism, sepsis/septicemia, septic shock, fever and malaise/asthenia have been reported following administration of epirubicin

Drug-related adverse events also occurred in the following systems:

Endocrine – amenorrhea and hot flashes

Cardiovascular – asymptomatic drops in left ventricular ejection fraction and congestive heart failure, ventricular tachycardia, bradycardia, atrioventricular (AV) block, bundle branch block

Ocular – conjunctivitis, keratitis

Other - infection, pneumonia, acute lymphocytic leukemia, acute myelogenous leukemia, hyperuricemia

Adverse Reactions in Early Breast Cancer Adjuvant Treatment:

On-Study Events
Integrated safety data are available from two studies (Studies MA.5 and GFEA-05 (FASG-05), see CLINICAL TRIALS, Early Stage Breast Cancer Studies) evaluating epirubicin-containing combination regimens in patients with early breast cancer. Of the 1260 patients treated in these studies, 620 patients received the higher-dose epirubicin regimen (FEC-100/CEF-120), 280 patients received the lower-dose epirubicin regimen (FEC-50), and 360 patients received CMF. Serotonin-specific anti-emetic therapy and colony-stimulating factors were not used in these trials. Clinically relevant acute adverse events are summarized in Table 1.

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

	% of Patients					
Event	**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**
Haematologic						
Leukopenia	80.3	58.6	49.6	1.5	98.1	60.3
Neutropenia	80.3	67.2	53.9	10.5	95.8	78.1
Anemia	72.2	5.8	12.9	0	70.9	0.9
Thrombocytopenia	48.8	5.4	4.6	0	51.4	3.6
Endocrine						
Amenorrhea	71.8	0	69.3	0	67.7	0
Hot flashes	38.9	4.0	5.4	0	69.1	6.4
Body as a Whole						
Lethargy	45.8	1.9	1.1	0	72.7	0.3
Fever	5.2	0	1.4	0	4.5	0
Gastrointestinal						
Nausea/vomiting	92.4	25.0	83.2	22.1	85.0	6.4
Mucositis	58.5	8.9	9.3	0	52.9	1.9
Diarrhea	24.8	0.8	7.1	0	50.7	2.8
Anorexia	2.9	0	1.8	0	5.8	0.3
Infection						
Infection	21.5	1.6	15.0	0	25.9	0.6
Febrile neutropenia	NA	6.1	0	0	NA	1.1
Ocular						
Conjunctivitis/keratitis	14.8	0	1.1	0	38.4	0
Skin						
Alopecia	95.5	56.6	69.6	19.3	84.4	6.7
Local toxicity	19.5	0.3	2.5	0.4	8.1	0

	% of Patients					
Event	**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**
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 + flurouracil NA = not available
Grade 1 or 2 changes in transaminase levels were observed but were more frequently seen with CMF than with CEF.

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

Table 2. Long-term Adverse Events in Patients with Early Breast Cancer (5-year follow-up data)*

	% of Patients		
Event	**FEC-100/CEF-120 (N = 620)**	**FEC-50 (N =280)**	**CMF (N=360)**
Cardiac events			
Asymptomatic drops in LVEF	1.8	1.4	0.8
CHF	1.5	0.4	0.3
AML/MDS			
AML	0.8	0	0.3
MDS	0	0	0

*In study MA.5 cardiac function was not monitored after 5 years. In study GFEA-05 (FASG-05) monitoring of cardiac function was optional.

Within the first 5 year follow-up period, 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.

Over the 10 year follow-up period for study GFEA-05 (FASG-05), the overall incidence of cardiac events in patients treated with FEC-100 remained similar to that reported in patients receiving FEC-50. There were, however, two new cases of decreased left ventricular ejection fraction reported in FEC-100 treated patients. Therefore, the incidence of decreased left ventricular ejection fraction was 1.1 % (3/280) in the FEC-50 group and 3% (8/266) in the FEC-100 group. No new cases of delayed CHF were reported. Thus the frequency of CHF remains at 0.4% (1/280) in the FEC-50 and at 1.1% (3/266) in the FEC-100 group. In a subset of patients from this study who were without disease at median follow up time of 102 months, a subsequent analysis of long term cardiac function identified 2 patients with CHF amongst the 85 FEC-100 patients evaluated (see reference 72). Cardiac function was not monitored after 5 years in MA.5

study.

No new cases of secondary leukemia were reported in the 10 year follow up for both MA.5 and GFEA-05 (FASG-05) trials.

Postmarketing Surveillance:

The following adverse reactions have been derived from spontaneous case reports, literature cases and clinical studies. The criteria for including these adverse reactions is based on the seriousness. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Myocardial infarction

Infections and infestations: sepsis/septic shock, pneumonia

Metabolism and nutrition disorders: hyperuricemia

Vascular disorders: haemorrhage, embolism arterial

Respiratory, thoracic and mediastinal disorders: interstitial lung disease, pulmonary embolism

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

Cutaneous: flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)

Hypersensitivity Reactions: urticaria, anaphylaxis, fever, chills, shock

Vascular: phlebitis, thrombophlebitis

Urological: red colouration of urine for 1 to 2 days after administration

DRUG INTERACTIONS

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see WARNINGS AND PRECAUTIONS). The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

Cimetidine increased the AUC of epirubicin by 50% when given for seven days, starting five days before chemotherapy. Cimetidine should be stopped prior to treatment with epirubicin.

DOSAGE AND ADMINISTRATION

Refer to SPECIAL HANDLING INSTRUCTIONS.

DOSAGE:

A variety of dose schedules have been used. The following recommendations are for use as a single agent or in combination with other chemotherapeutic agents.

Dosage is usually calculated on the basis of body surface area. The lower dose should be given to patients with inadequate marrow reserves due to prior therapy or neoplastic marrow infiltration. Standard starting doses and regimens have been used in the elderly.

Hepatic Dysfunction. As epirubicin is extensively metabolized by the liver and excreted primarily by the biliary system, its dosage must be reduced in patients with impaired liver function indicated by elevated bilirubin or serum AST values as follows: Serum bilirubin 21-51 µmol/L or AST 2 to 4 times upper limit of normal - give ½ of recommended starting dose; Serum bilirubin > 51 µmol/L or AST > 4 times upper limit of normal - give ¼ of recommended starting dose. Patients with severe hepatic impairment should not receive epirubicin (see CONTRAINDICATIONS).

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

Other Special Populations. Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients or patients with neoplastic bone marrow infiltration (see WARNINGS AND PRECAUTIONS). Standard starting doses and regimens have been used in the elderly.

CARCINOMA OF THE BREAST

Early Breast Cancer-Adjuvant Treatment

Breast cancer has been managed using epirubicin in combination with various chemotherapeutic agents. The recommended adjuvant treatment of early breast cancer should employ a cyclophosphamide, epirubicin, and 5-fluorouracil combination regimen (CEF 120) in a cycle to be repeated every 4 weeks for 6 cycles as follows:

- cyclophosphamide 75 mg/m^2 p.o. on days 1 to14,
- epirubicin 60 mg/m^2 i.v. on days 1 and 8, and
- 5-fluorouracil 500 mg/m^2 i.v. days 1 and 8.

Metastatic Breast Cancer

Single Agent: The most commonly used dosage schedule of Epirubicin Hydrochloride Injection in metastatic breast cancer, when employed as a single agent for adults, is 75-90 mg/m^2 administered at 21-day intervals. The recommended single dose may be divided over 2 successive days. An alternative weekly dosage schedule of 12.5 to 25 mg/m^2 has been used and has been reported to produce less clinical toxicity than higher doses given every three weeks.

Combination Therapy: In metastatic breast cancer, epirubicin can be used in combination with cyclophosphamide and 5-fluorouracil (FEC), at a dose of 50 mg/m^2.

SMALL CELL LUNG CANCER
Single Agent: Epirubicin Hydrochloride Injection, as a single agent, can be used at 90-120 mg/m^2 administered every 3 weeks.

Combination Therapy: Epirubicin has been used in several different combinations with other antineoplastic agents at doses ranging from 50-90 mg/m^2. The following combinations have proven effective: Epirubicin in combination with either cisplatin or ifosfamide; epirubicin with cyclophosphamide and vincristine (CEV); epirubicin with cyclophosphamide and etoposide (CEVP-16) and epirubicin with cisplatin and etoposide.

NON-SMALL CELL LUNG CANCER:
Single Agent: Epirubicin Hydrochloride Injection, as a single agent, can be used at doses of 120-150 mg/m^2 administered day 1, every 3-4 weeks.

Combination Therapy: Epirubicin, in combination with etoposide, cisplatinum, mitomycin, vindesine and vinblastine, can be used at doses of 90-120 mg/m^2 administered day 1, every 3-4 weeks.

NON-HODGKIN'S LYMPHOMA
Single Agent: Epirubicin Hydrochloride Injection, as a single agent, can be used at doses of 75-90 mg/m^2 at 21 day intervals.

Combination Therapy: Epirubicin at doses of 60-75 mg/m^2 can be used in combination with cyclophosphamide, vincristine and prednisone with or without bleomycin (replacing doxorubicin in the CHOP, CHOP-Bleo or BACOP regimens) for the treatment of newly diagnosed non-Hodgkin's lymphoma.

HODGKIN'S DISEASE
Combination Therapy: Epirubicin, in combination with bleomycin, vinblastine and dacarbazine, can be used at 35 mg/m^2 every 2 weeks or 70 mg/m^2 every 3-4 weeks (replacing doxorubicin in the ABVD regimen).

OVARIAN CANCER
Single Agent: In patients with prior therapy, epirubicin can be used as single agent at doses of 50-90 mg/m^2 at 3-4 week intervals.

Combination Therapy: In patients with prior therapy epirubicin can be used in combination at doses of 50-90 mg/m^2 at 3-4 week intervals. Epirubicin at doses of 50-90 mg/m^2 in combination with cisplatin and cyclophosphamide can be used for initial therapy of ovarian cancer repeated at 3-4 week intervals.

GASTRIC CANCER
Single Agent: Epirubicin, as a single agent, can be used for the treatment of locally unresectable or metastatic gastric carcinoma at doses of 75-100 mg/m^2.

Combination Therapy: Epirubicin, at a dose of 80 mg/m^2 can be used in combination with fluorouracil for the treatment of locally unresectable or metastatic gastric carcinoma.

ADMINISTRATION:

Care in the administration of Epirubicin Hydrochloride Injection will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of Epirubicin Hydrochloride Injection extravasation may occur with or without an accompanying stinging or burning sensation even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the injection or infusion should be immediately terminated and restarted in another vein. If it is known or suspected that subcutaneous extravasation has occurred, the following steps are recommended:

1. Attempt aspiration of the infiltrated Epirubicin Hydrochloride Injection solution.

2. Local intermittent application of ice for up to 3 days.

3. Elevation of the affected limb.

4. Close observation of the lesion.

5. Consultation with a plastic surgeon familiar with drug extravasation if local pain persists or skin changes progress after 3 to 4 days. If ulceration begins, early wide excision of the involved area should be considered.

Before Epirubicin Hydrochloride Injection administration, visually inspect the solution for particulate matter and discoloration. If any discoloration or particulate matter is observed, do not use the product. Epirubicin Hydrochloride Injection should be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Solution USP (0.9%) or 5% Dextrose Solution USP. The tubing should be attached to a Butterfly® needle or other suitable device and inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. To minimize the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. The infusion time should be not less than 3 to 5 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 (see WARNING AND PRECAUTIONS). Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Unless specific compatibility data are available, mixing Epirubicin Hydrochloride Injection with other drugs is not recommended.

Epirubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated.

For Safe Preparation and Handling of Epirubicin Hydrochloride Injection refer to "SPECIAL HANDLING INSTRUCTIONS".

OVERDOSAGE

Acute overdosage with Epirubicin Hydrochloride Injection may cause an acute myocardial dysfunction within 24 hours. Pronounced mucositis, leukopenia and thrombocytopenia could be observed within 7-14 days. Treatment of acute overdosage consists of hospitalization of the severely myelosuppressed patient, platelet and granulocyte transfusions, antibiotics, and symptomatic treatment of mucositis.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

The mechanism of action of epirubicin, although not completely elucidated, appears to be related to its ability to bind to nucleic acids by intercalation of the planar anthracycline nucleus with the DNA double helix.

Binding to cell membranes as well as to plasma proteins may also be involved. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity, mutagenesis and chromosomal aberrations.

Animal studies have shown activity in a wide spectrum of experimental tumours, immunosuppression, mutagenic and carcinogenic properties in rodents, and a variety of toxic effects, including myelosuppression in all species and atrophy of the seminiferous tubules of testes in rats and dogs.

Data from different animal species and ***in vitro*** models have shown that epirubicin is less toxic,

and in particular less cardiotoxic than doxorubicin.

At equally effective doses, epirubicin produces less severe non-haematologic side effects such as vomiting and mucositis, than doxorubicin.

Early Stage Breast Cancer Studies:

Two randomized, open-label, multi center studies evaluated epirubicin 100 to 120 mg/m^2 in combination with cyclophosphamide and fluorouracil in adjuvant treatment of axillary-node-positive breast cancer with no evidence of distant metastatic disease. (See CLINICAL TRIALS for complete study descriptions and overall results; see ADVERSE REACTIONS.)

Study MA.5 evaluated 120 mg/m^2 doses of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen) versus a CMF (methotrexate) regimen in pre- and peri-menopausal women.

Study GFEA-05 (FASG-05) evaluated 100 mg/m^2 doses of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100) or lower-dose FEC-50 in pre- and post-menopausal women.

In the pivotal trial MA.5, the Cox proportional model showed that node number is a significant (p=0.0001) outcome predictor overall (conditional risk ratio of 1.7 for $\geq$ 4 versus < 3 involved nodes). Non-significant trends indicate that the CEF treatment may show superiority over CMF in patients with $\geq$ 4 nodes than those with < 3. The trial was insufficiently powered to demonstrate a subset difference; it must be borne in mind that the majority of patients (61%) in both treatments had 1-3 positive nodes, yet CEF-120 still produced overall advantages in relapse free survival (RFS) and overall survival (OS) (see below and CLINICAL TRIALS). Nonetheless, CEF versus CMF RFS in the <3 node group was 68 vs. 62%, while in the $\geq$ 4 node group the values were 52 vs. 39%.

In the supporting trial GFEA-05 (FASG-05), similar improvements in RFS and OS were observed in both pre- and postmenopausal women treated with FEC-100 compared to FEC-50.

Overall efficacy results for the two studies are shown in Table 4 (see CLINICAL TRIALS). The median follow-up time in the MA.5 study was 8.8 years (range: 0.2 to 12.1 years) and 8.7 years (range: 0.7 to 12.1 years) for the CEF and CMF treatment groups, respectively. In MA.5, the CEF-120 therapy demonstrated superior RFS to CMF, both over the 5- and 10-year follow-up. The overall reduction in risk of relapse was 24% over 5 years and 22% over 10 years. The 5- and 10-year OS were also greater for the epirubicin-containing CEF-120 regimen than for the CMF regimen. The overall relative reduction in the risk of death was 29% over 5 years and 18% over 10 years.

Pharmacokinetics:

Pharmacokinetic studies show an initial rapid elimination of the parent compound from plasma.

The terminal half-life of elimination of the parent drug from plasma approximates 30-40 hours in humans. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours. Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged drug.

Impairment of hepatic function results in higher plasma levels.

Distribution studies in the rat have shown that epirubicin does not appear to cross the blood-brain barrier.

STORAGE AND STABILITY

Epirubicin Hydrochloride Injection should be stored under refrigeration (2 - 8ºC), and retained in original carton until time of use. Do not freeze. Protect from light. Unused solution should be discarded.

Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of initial entry because of the potential for microbial contamination.

Incompatibility:

Unless specific compatibility data are available, Epirubicin Hydrochloride Injection should not be mixed with other drugs.

Contact with any solution of an alkaline pH should be avoided, as it will result in hydrolysis of the drug. Epirubicin should also not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

SPECIAL HANDLING INSTRUCTIONS

Preparation and Handling:

1. Personnel should be trained in good technique for reconstitution and handling. Pregnant staff should be excluded from working with this drug.

2. Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II) and the work surface should be protected by disposable, plastic-backed absorbent paper.

3. Personnel handling epirubicin solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks. If epirubicin solutions contact the skin or mucosa, the area should be washed with soap and water or sodium bicarbonate immediately. Do not abrade the skin by using a scrub brush and always wash hands after removing gloves.

4. In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes, proceed to a physician for medical evaluation.

5. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

6. Directions for Dispensing from Pharmacy Bulk Vial

   The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only.

   Entry into the vial must be made with a sterile dispensing device such as the Econ-O-Set® Sterile Transfer System[1]. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as increasing the potential for microbial and particulate contamination.

   Swab the vial stopper with an antiseptic solution. Following carefully the manufacturer's instructions, insert the device into the vial. Withdraw contents of vial into syringes, using aseptic technique. Discard any unused portion within eight hours of initial entry.

Disposal:

1. Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

2. All needles, syringes, vials and other materials which have come in contact with epirubicin should be segregated in plastic bags, sealed, and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

3. If incineration is not available, epirubicin hydrochloride may be detoxified by adding sodium hypochlorite solution (household bleach) to the vial, in sufficient quantity to decolourize the epirubicin, care being taken to vent the vial to avoid a pressure build-up of the chlorine gas which is generated. Dispose of detoxified vials in a safe manner.

[1] Distributed by International Medication Systems of Canada, Ltd.

Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution and disposable equipment in a safe manner. Thoroughly wash non-disposable equipment in soap and water.

Spillage/Contamination:

Wear gloves, mask, protective clothing. Treat spilled liquid with sodium hypochlorite solution. Carefully absorb solution with gauze pads or towels, wash area with water and absorb with gauze or towels again and place in polyethylene bag; seal, double bag and mark as hazardous waste. Disposal of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean-up should wash with soap and water.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Epirubicin Hydrochloride Injection is available in 25 mL and 100 mL Amber glass vials, each vial containing 2 mg/mL of epirubicin hydrochloride.

The 25 mL vials are packaged and supplied in single vial cartons.

The 100 mL Pharmacy Bulk Vials are packaged and supplied in single vial cartons.

NOTE:
THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM. THE PHARMACY BULK VIAL IS INTENDED FOR SINGLE PUNCTURE, MULTIPLE DISPENSING AND FOR INTRAVENOUS USE ONLY.

Entry into the vial must be made with a suitable, sterile transfer or dispensing device. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as it may increase the potential for microbial and particulate matter contamination.

In a suitable work area such as a laminar flow hood, swab the vial stopper with an antiseptic solution. Insert the device into the vial. Withdraw contents of the vial into sterile syringes using strict aseptic techniques. Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of the initial entry because of the potential for microbial contamination. Discard any unused portion. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature or 48 hours when refrigerated from the time of the initial entry into the Pharmacy Bulk Vial.

Composition:

Epirubicin Hydrochloride Injection is a sterile, ready-to-use red-orange solution. It is supplied in glass vials as a 2 mg/mL isotonic, non-preserved solution.

25 mL Vials - Each mL contains 2 mg of epirubicin hydrochloride, 9 mg of Sodium Chloride USP, Water for Injection USP and Hydrochloric Acid for pH adjustment.

100 mL Vials - Each mL contains 2 mg of epirubicin hydrochloride, 9 mg of Sodium Chloride USP, Water for Injection USP and Hydrochloric Acid for pH adjustment.

PART II: SCIENTIFIC INFORMATION

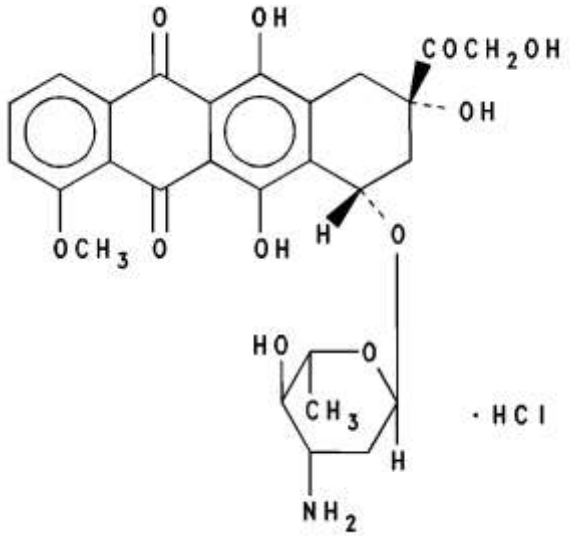
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: epirubicin hydrochloride

Chemical Name: (8S-cis)-10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5, 12-naphthacenedione hydrochloride

Structural Formula:



Molecular Formula: $C_{27}H_{29}NO_{11}\bullet HCl$

Molecular Weight: 579.98 g/mol

Description:

Epirubicin hydrochloride is a semisynthetic anthracycline cytotoxic antibiotic in which the sugar moiety differs from the natural daunosamine (amino sugar present in doxorubicin) in that steric configuration of the hydroxyl bearing C-4 is inverted, thus forming the L-arabino configuration instead of the L-lyxo. The anthracycline ring is lipophilic. The saturated end of the ring system contains hydroxyl groups adjacent to the amino sugar producing a hydrophilic centre. The molecule is amphoteric, containing acidic function in the phenolic ring groups and a basic function in the sugar amino group.

It is a dark red crystalline powder, soluble in water, methanol and ethyl alcohol (50°C). It is practically insoluble in acetone, chloroform and methylene chloride. Epirubicin hydrochloride has a melting point of 173-177°C, pKa in water of 7.7, and pH of 4-5.5 in a 0.5% w/v solution in water.

CLINICAL TRIALS

Early Stage Breast Cancer Studies (see ADVERSE REACTIONS)

Two randomized, open-label, multi center studies evaluated the use of epirubicin 100 to 120 mg/m^2 in combination with cyclophosphamide and fluorouracil for the adjuvant treatment in 1281 women with:

- axillary-node-positive breast cancer,
- no evidence of distant metastatic disease (Stage II or III), and
- no T4 tumors.

Study MA.5 evaluated 120 mg/m^2 of epirubicin per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). Pre- and peri-menopausal women with one or more positive lymph nodes were randomized to either the CEF-120 regimen or a CMF regimen.

Study GFEA-05 (FASG-05) evaluated the use of 100 mg/m^2 of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100). Pre- and post-menopausal women were randomized to either the FEC-100 or lower-dose FEC-50 regimens. Eligible patients were either required to have 4 nodes involved with tumour or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptors and a histologic tumour grade of 2 or 3.

Table 3 shows the treatment regimens that the patients received.

Table 3. Treatment Regimens Used in Early Breast Cancer Phase 3 Studies

	Treatment Groups	Agent	Regimen
MA.5[1] N=716	**CEF-120** (total, 6 cycles)[2] N=356	Cyclophosphamide	75 mg/m^2 PO d 1-14, q 28 days
		Epirubicin	60 mg/m^2 IV d 1 & 8, q 28 days
		Fluorouracil	500 mg/m^2 IV d 1 & 8, q 28 days
	CMF (total, 6 cycles) N=360	Cyclophosphamide	100 mg/m^2 PO day 1-14, q 28 days
		Methotrexate	40 mg/m^2 IV day 1 & 8, q 28 days

	Treatment Groups	Agent	Regimen
		Fluorouracil	600 mg/m^2 IV, d 1 & 8, q 28 days
GFEA-05 (FASG-05)[3] N=565	**FEC-100** (total, 6 cycles) N=276	Fluorouracil	500 mg/m^2 IV day 1, q 21 days
		Epirubicin	100 mg/m^2 IV day 1, q 21 days
		Cyclophosphamide	500 mg/m^2 IV day 1, q 21 days
-	**FEC-50** (total, 6 cycles) N=289	Fluorouracil	500 mg/m^2 IV day 1, q 21 days
		Epirubicin	50 mg/m^2 IV day 1, q 21 days
	Tamoxifen 30 mg daily x 3 years, postmenopausal women, any receptor status.	Cyclophosphamide	500 mg/m^2 IV day 1, 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 fluroquinolone for the duration of their chemotherapy.
[3] All women were to receive breast irradiation after the completion of chemotherapy.

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 are described in terms of the outcomes over 5 and 10 years.

MA.5 results: 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. The median follow-up time was 8.8 years (range: 0.2 to 12.1 years) and 8.7 years (range: 0.7 to 12.1 years) for the CEF and CMF treatment groups, respectively. The epirubicin-containing combination therapy (CEF-120) demonstrated superior RFS to CMF, both over the 5- and 10-year follow-up (Table 4). The overall reduction in risk of relapse was 24% over 5 years and 22% over 10 years. The 5- and 10-year OS were also greater for the CEF-120 regimen than for the CMF regimen (Table 4). The overall relative reduction in the risk of death was 29% over 5 years and 18% over 10 years.

GFEA-05 (FASG-05) results: 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 median follow-up time was 7.7 years (range: 0.3 to 12.5 years) and 8.7 years (range: 0.2 to 12.7 years) in the FEC-50 and FEC-100 treatment groups, respectively. Patients treated with the higher-dose epirubicin regimen (FEC- 100) had a significantly longer RFS and OS over 5- and 10-years (Table 4) than patients given the lower dose

regimen (FEC-50). The overall reduction in risk of relapse was 32% over 5 years and 22% over 10 years. The relative reduction in the risk of death was 31% over 5 years and 25% over 10 years.

Although the trials were not powered for subgroup analyses, in the MA-5 study improvement in favor of CEF-120 vs. CMF were observed over 5- and 10-years in RFS and OS both in patients with 1-3 node positive and those with $\geq$ 4 node positive tumor involvement. In the GFEA-05 (FASG-05) study, improvements in RFS and OS were observed over 5- and 10-years in both pre- and post-menopausal women treated with FEC-100 compared to FEC-50.

Efficacy results for the two studies are shown in Table 4.

Table 4. Efficacy Results from Early Breast Cancer Phase 3 Studies*

	MA.5 Study		GFEA-05 (FASG-05) Study	
	CEF-120 N = 356	CMF N = 360	FEC-100 N = 276	FEC-50 N = 289
RFS over 5 yrs (%)	62	53	65	52
Log-Rank Test	(stratified p = 0.013)		(p = 0.007)	
OS over 5 yrs (%)	77	70	76	65
Log-Rank Test	(stratified p = 0.043) (unstratified p = 0.13)		(p = 0.007)	
RFS over 10 yrs (%)	51	44	49	43
Log-Rank Test (stratified)	(p = 0.017)		(p = 0.040)	
OS over 10 yrs (%)	61	57	56	50
Log-Rank Test (stratified)	(p = 0.100)		(p = 0.023)	
*Based on Kaplain-Meier estimates				

The Kaplain-Meier curves for RFS and OS from Study MA.5 are shown in Figures 1 and 2 and those for Study GFEA-05 (FASG-05) are shown in Figure 3 and 4.

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

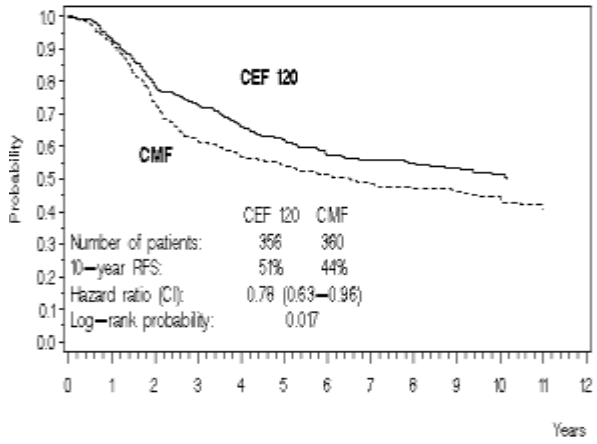


Figure 2. Overall Survival in Study MA-5

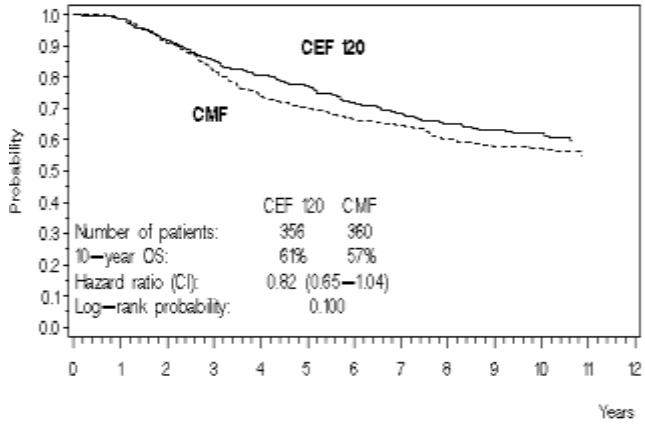


Figure 3. Relapse-Free Survival in Study GFEA-05 (FASG-05)

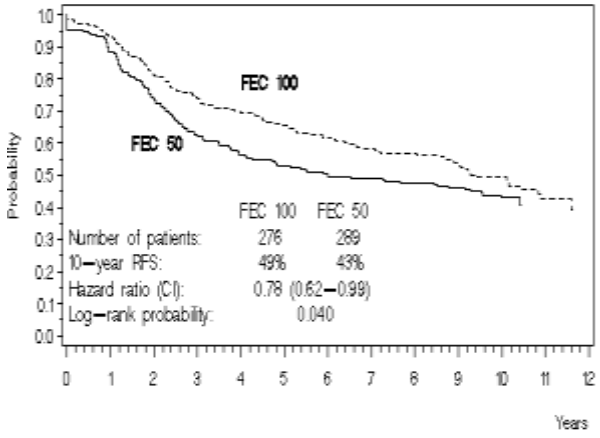
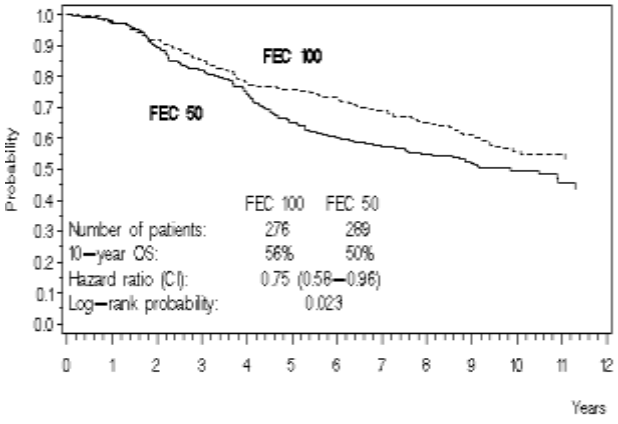


Figure 4. Overall Survival in Study GFEA-05 (FASG-05)



DETAILED PHARMACOLOGY

The *in vitro* cytotoxicity of epirubicin, compared to doxorubicin, was investigated using the HeLa cloning efficiency test, the human tumour stem cell assay and the inhibition of mouse embryo fibroblast proliferation test. In the first test, epirubicin had less activity than doxorubicin. In the other two tests the activity of the two compounds was similar.

The antitumoural activity of epirubicin was compared with doxorubicin on various mouse experimental tumours. Administered i.p. or i.v. as a single injection (sarcoma 180 ascites, leukemia L1210, leukemia P388, Gross leukemia), the two compounds had the same antitumour effect at the same dose. One sub-line of leukemia P388 resistant to doxorubicin showed cross- resistance to epirubicin. Administered i.v. and at the same dose, the two compounds had exactly the same effect on solid sarcoma 180 and on both advanced and early mammary carcinoma.

The antitumoural effect of epirubicin was slightly greater than that of doxorubicin on Lewis lung carcinoma and MS-2 sarcoma lung metastases and also on MSV-induced rhabdomyosarcoma and on colon 38 adenocarcinoma.

Epirubicin was found active on mammary carcinoma, melanoma, epidermoid carcinoma of the lung and soft tissue sarcoma, transplanted to nude mice.

Epirubicin was found active against breast, lung, prostate and ovarian tumours transplanted in nude mice; it showed particularly good activity against melanomas. No statistically significant effect was observed against colorectal human tumours transplanted into nude mice.

Pharmacokinetic studies in man show an initial rapid elimination of the parent compound from plasma. The terminal half-life of elimination of the parent drug from plasma approximates 30-40 hours. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours. Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubincol.

Glucuronidation distinguishes epirubicin from doxorubicin and may account for its reduced toxicity. Other metabolites found are aglycones of 7-deoxydoxorubicin and 7- deoxydoxorubinicol. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel to those of the unchanged drug.

TOXICOLOGY

The acute toxicity of epirubicin i.v. was studied in the mouse, rat and dog.

In the mouse, single doses caused dose-dependent deaths between the 4th and 180th day after injection. Calculated at stabilization, the LD_{50} was 15.06 mg/kg.

In the rat, single doses of epirubicin produced dose-dependent mortality between the 4th and

15th day after injection. Calculated at stabilization, the LD_{50} was 13.95 mg/kg.

In the dog, single doses were lethal at 2 mg/kg, while the lower dose (1 mg/kg) can be held to be just within the safety limit.

Chronic toxicity studies were carried out in the rabbit and in the dog after i.v. courses of three consecutive days per week for a total of 6 weeks on the rabbit and 6 and 13 weeks in the dog. The results showed that, in the rabbit, the pharmacological-toxicological mechanism of action of epirubicin is very similar to that of doxorubicin. In qualitative terms, epirubicin is very similar to that of doxorubicin. In quantitative terms, epirubicin was approximately one-third less toxic than doxorubicin with respect to systemic toxicity and myocardial toxicity.

In the dog, the two drugs had the same toxicity profile. The safe dose of epirubicin can be set at 0.1 mg/kg in this species.

In vitro cardiotoxicity tests showed that epirubicin was less cardiotoxic than doxorubicin (on isolated rabbit heart and guinea pig heart); unlike doxorubicin, sometimes it had no effect at all on myocardial cells from newborn mice.

In vivo cardiotoxicity tests showed that in all the animal species tested (mouse i.v., rat i.p., rabbit i.v.) epirubicin was appreciably less cardiotoxic than doxorubicin.

Ultrastructural studies of myocardial tissue from hamsters treated i.p. with epirubicin and doxorubicin showed that the two drugs produce similar alterations in the same length of time. Carcinogenesis tests *in vivo* run in newborn rats treated with epirubicin s.c. showed that the drug had considerable carcinogenic activity. Mutagenic activity of epirubicin was investigated in various *in vitro* and *in vivo* tests. In the *in vitro* and *in vivo* tests, *Schizosccharomyces pombe* P1, epirubicin showed no mutagenic activity; it was mutagenic, however, *in vitro* on *Salmonella typhimurium*.

Epirubicin has not shown teratogenic effects in rats or rabbits; embryotoxicity and/or abortions were seen in both species only at very high doses.

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PART III: CONSUMER INFORMATION

[Pr]Epirubicin Hydrochloride Injection

This leaflet is part III of a three-part "Product Monograph" published when Epirubicin Hydrochloride Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Epirubicin hydrochloride injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Epirubicin Hydrochloride Injection and cancer treatment:

What is Epirubicin Hydrochloride Injection used for:
Epirubicin Hydrochloride Injection alone or in combination with other anticancer drugs is used in the treatment of:

- Metastatic breast cancer
- Small cell lung cancer, advanced non-small cell lung cancer
- Stage III and IV ovarian cancer
- Metastatic and locally unresectable gastric carcinoma

Epirubicin Hydrochloride Injection in combination with other anticancer drugs is also used in the adjuvant treatment of early stage of breast cancer for pre- and peri-menopausal women.

What it does:
Epirubicin Hydrochloride Injection is a chemotherapy drug, often used in combination with other drugs to kill cancer cells. Most chemotherapy agents (including Epirubicin Hydrochloride Injection) work by killing rapidly dividing cells, such as cancer cells. This action can affect normal cells as well.

In breast cancer, it can be used following surgery and/or radiation as adjuvant or additional therapy. Here, it is used to kill cancer cells that have 'escaped' the tumour and could spread to other parts of the body (like the bones, liver, or lungs), where the cancer can grow again and recur. If breast cancer has spread to the lymph nodes in the axilla (armpit), there is higher chance of recurrence if no treatment is given. (The axillary lymph nodes normally drain fluid from the breast and arm.) The extent of the cancer cell spreading may be a factor when a chemotherapy regimen is chosen.
BEFORE STARTING TREATMENT YOU AND YOUR DOCTOR SHOULD DISCUSS TREATMENT OPTIONS BEST SUITED TO YOU, TAKING INTO CONSIDERATION YOUR CONDITION AND OTHER HEALTH CONCERNS THAT YOU MAY HAVE.

In other cancers, chemotherapy can be used to reduce tumour size, or stop them from growing. Understand why your doctor has chosen the particular chemotherapy regimen to be used, and know all the risk and benefits before starting therapy.

When it should not be used:
Do not use the drugs if you:

- are allergic to epirubicin or any of the ingredients of the drug or its container (see **What is in your medication)**,
- are allergic to other anthracyclines or anthracediones such as doxorubicin, daunorubicin, mitoxanthrone or mitomycin C.
- have persistent low blood count (myelosuppression)
- have severe liver impairment
- have severe heart disease
- have had a recent heart attack
- have irregular heartbeat
- have a history of severe cardiac disease
- have been treated with a maximum cumulative dose of epirubicin and/or other anthracyclines and anthracenediones

What the medicinal ingredient is:
Epirubicin hydrochloride.

What the non-medicinal ingredients are:
Sodium chloride, hydrochloric acid, and water for injection

What dosage form it comes in:
Epirubicin Hydrochloride Injection 2 mg/mL is available in 25 mL and 100 mL glass vials.

WARNINGS AND PRECAUTIONS

Severe local tissue degradation caused by fluid leakage from the veins to the surrounding tissues during administration

Cardiac toxicity, manifested in its most severe form by potentially fatal heart failure

A severe decrease in the ability of the bone marrow to produce blood cells

Epirubicin Hydrochloride Injection should be given under the supervision of a doctor experienced with the use of anticancer drugs.

Epirubicin Hydrochloride Injection should not be given to patients with the following conditions:

- **A low blood count (bone marrow suppression induced by previous drug therapy or radiotherapy);**
- **A heart disease and/or previous treatment with anthracyclines (cardiotoxic drugs)**

Before using Epirubicin Hydrochloride Injection, tell your doctor if any of the following applies to you:

- if you have or have experienced a sensitivity or allergic reaction to epirubicin or any other component of the product (see ***what is in your medication***), other anthracyclines or anthracenediones such as doxorubicin hydrochloride, daunorubicin hydrochloride, mitoxantrone or mitomycin C.
- if you have low blood cell counts due to a decreased ability of the bone marrow to produce blood cells
- if you have severe liver disease
- if you have a heart disease, recent heart attack or irregular heartbeat
- if you are taking other drugs (including calcium channel blockers) or have been previously treated with Epirubicin Hydrochloride Injection or other anti-cancer drugs, including anthracyclines (cardiotoxic drugs).

As Epirubicin Hydrochloride Injection may be harmful to an unborn child, women should be advised to avoid becoming pregnant. Effective contraceptive methods should be used.

Tell your doctor right away if you become pregnant during treatment. If you have been nursing, you should stop before starting treatment with Epirubicin Hydrochloride Injection. Ask your baby's doctor to recommend a formula that would be best for your baby.

INTERACTIONS WITH THIS MEDICATION

Administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy should be avoided.

PROPER USE OF THIS MEDICATION

How is Epirubicin Hydrochloride Injection *given?*
Some patients may receive Epirubicin Hydrochloride Injection through a vein in the arm ("intravenously" or "IV") by their doctor or nurse, usually in the hospital, outpatient department or clinic.

If you are getting many injections over several weeks or months, for your convenience, your doctor may insert a catheter (thin tube) or port into a large vein in your body that is placed there as long as it is needed. Medicines get injected through the catheter or port rather than directly into a vein.

How much time does it take to get a treatment with* Epirubicin Hydrochloride Injection*?
It usually takes about 5 minutes to inject *Epirubicin Hydrochloride Injection*. However, you may get other medicines before or after *Epirubicin Hydrochloride Injection*, so your entire treatment may last an hour or longer.

How long will I need treatment?
Your doctor will determine the length of your treatment based on your treatment goals, the medicines you receive, and how your body responds to those medicines. Adjuvant chemotherapy for breast cancer usually lasts 3-6 months, however.

Chemotherapy is usually given in cycles that include rest periods between treatments. The rest periods give your body a chance to build healthy new cells and regain your strength before your next treatment. Epirubicin Hydrochloride Injection is given in treatment cycles of 21 days or 28 days. You may receive one dose of Epirubicin Hydrochloride Injection every three or four weeks (on Day 1 of the cycle). Or, you may receive Epirubicin Hydrochloride Injection in two doses - one dose on Day 1 of the cycle, and another dose on Day 8.
Your treatment cycle will depend on your medical condition and the other chemotherapy medicines you are getting.

Will I be able to work?
Some people work full time, while others work part time or wait until their chemotherapy treatments are finished. It depends on the type of job you have and the side effects you experience.

Is it okay to become pregnant or nurse a baby?
No. *Epirubicin Hydrochloride Injection* can be harmful to an unborn child. If there is any possibility that you may become pregnant, ask your doctor about using birth control to prevent pregnancy during your treatment with Epirubicin Hydrochloride Injection. Tell your doctor right away if you become pregnant during treatment. If you have been nursing, you should stop before starting treatment with Epirubicin Hydrochloride Injection. Ask your baby's doctor to recommend a formula that would be best for your baby.

What should men consider when taking Epirubicin Hydrochloride Injection?
Men undergoing treatment with epirubicin should use effective contraceptive methods.

What happens after treatment?
After you have completed all your chemotherapy treatments, your doctor will check you regularly to make sure the cancer has not returned.

Overdose:

If you think you, or a person you are caring for, have taken too much Epirubicin Hydrochloride Injection, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms

Missed Dose:
If you miss your scheduled treatment with the drug, contact your doctor as soon as possible to schedule your next treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Epirubicin Hydrochloride Injection may cause side effects. Everyone reacts differently to chemotherapy and not all people will experience every side effect.

Common side effects include:

- hair loss, which is temporary and usually starts to grow back within 2 or 3 months after you have finished your treatments.
- increased risk of infection, as a result of low white blood cell count. The signs of infection include fever over 38°C (100°F), chills or sweating, sore throat or coughing, redness or swelling around a cut, wound or a catheter site, a burning feeling when you urinate, unusual vaginal itching or discharge.
- nausea and vomiting.
- fatigue, or feeling tired.
- mouth sores.
- Epirubicin Hydrochloride Injection is a red-orange coloured liquid and will make your urine turn red for a few days after treatment.

The kinds of side effects, how often they occur, and how bad they may be could be related to the dose of chemotherapy, or the regimen used.

Rare side effects include:

- Damage to the heart muscle, which can cause symptoms such as shortness of breath, swelling in the ankles, and fluid retention. If you have these symptoms, call your doctor right away. There are medicines to treat this condition.
- Secondary leukemia (less than 1% of patients) up to 5 years after treatment with Epirubicin Hydrochloride Injection.

The chances of developing heart damage or leukemia appear to be related to either how much chemotherapy you have received, or the dose of Epirubicin Hydrochloride Injection used. Be sure you discuss the risks and benefits of various chemotherapy options with your doctor, and understand the side-effects both immediate and long-term that you could have from your treatment before you start therapy.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
• **Low white blood cell count** and symptoms such as increased infection, fever > 38°C, chills or sweating, sore throat, mouth sores, burning feeling when urinating, unusual vaginal itching or discharge		√
• **Anemia** (reduced red blood cell) and symptoms such as feeling weak, dizzy, shortness of breath		√
• **Injection site reactions** such as pain, sores, burning		√
• **Increased bleeding** with symptoms such as dark urine or dark/bloody stool, unexplained bruising		√
• **Cardiovascular problems** with symptoms such as irregular heartbeat, chest pain, swelling of the ankle, shortness of breath / cardiac problems		√
• **Bowel inflammation** (colitis) or, digestive tract bleeding and symptoms such as bloody stools, bloody vomit		√

This is not a complete list of side effects. For any unexpected effects while taking Epirubicin Hydrochloride Injection, contact your doctor or pharmacist.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Epirubicin Hydrochloride Injection

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling 1-888-318-0234.

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