

## ☐ Epirubicin Hydrochloride Injection Antineoplastic Agent

### CAUTION

Epirubicin Hydrochloride Injection is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs (see **WARNINGS AND PRECAUTIONS** section). Blood counts and hepatic function tests should be performed regularly. Irreversible cardiac toxicity may occur as the cumulative dose approaches 1000 mg/m<sup>2</sup>. 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<sup>2</sup>.

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	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile solution for injection/2 mg/mL	Not Applicable. <i>For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

### 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 tumor 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.

In addition, several other solid tumors have shown responsiveness to epirubicin hydrochloride but data are not yet sufficient to justify specific recommendations.

Epirubicin Hydrochloride Injection does not contain lactose and hence may be used in patients with lactose allergy.

### 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 antitumor 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** section).

### WARNINGS AND PRECAUTIONS

#### 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 therapy.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m<sup>2</sup> to 1000 mg/m<sup>2</sup> 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. 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 at a lower total dose than previously untreated patients and, therefore, should be carefully monitored. The total dose of epirubicin hydrochloride 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<sup>2</sup> 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 are presently not considered indications for suspension of epirubicin hydrochloride therapy.

Epirubicin hydrochloride 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 hydrochloride. If test results indicate a change in cardiac status associated with epirubicin hydrochloride 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** section) leukopenia is transient, reaching its nadir 10 to 14 days after treatment, with recovery usually occurring by the 21<sup>st</sup> day. White blood cell counts as low as 1000/mm<sup>3</sup> are to be expected during treatment with epirubicin hydrochloride.

Red blood cell and platelet levels should be monitored since they may also be depressed. Hematologic toxicity may require dose reduction or delay or suspension of epirubicin hydrochloride therapy. Persistent myelosuppression may result in infection or hemorrhage.

Epirubicin hydrochloride 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.

While treatment with high doses of epirubicin (e.g.,  $\geq 90$  mg/m<sup>2</sup> every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m<sup>2</sup> 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.

#### 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 **DOSE AND ADMINISTRATION** section). Patients with severe hepatic impairment should not receive epirubicin (see **CONTRAINDICATIONS** section).

#### Renal Function

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

#### 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 to 3 years) latency period (see below and in Table 2 under **ADVERSE REACTIONS** section).

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** section of the full Product Monograph). As of 31 December 2001, 28 (0.39%) of the 7110 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 7110 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<sup>2</sup>), the incidence of AML/MDS was 1.1% at 5 years with no additional cases observed during the second 5 years (years 6 to 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 must not be administered by intramuscular or subcutaneous injection.

Severe local tissue necrosis can occur if epirubicin hydrochloride 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 **DOSE AND ADMINISTRATION** section). 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 hydrochloride 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** section). 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 hydrochloride imparts a red colouration to the urine for 1 or 2 days after administration. Patients should be advised to expect this during active therapy.

#### Special Populations

##### Usage in Pregnancy:

There is no conclusive information about epirubicin adversely affecting human fertility, or causing teratogenesis; however, at high doses, epirubicin hydrochloride 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 pregnancy.

Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If epirubicin hydrochloride 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.

#### Monitoring and Laboratory Tests:

Initial treatment with epirubicin hydrochloride requires close observation of the patient and extensive laboratory monitoring. Like other cytotoxic drugs, epirubicin hydrochloride 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 alkalization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Epirubicin hydrochloride 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, 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 **CONSUMER INFORMATION**.

#### ADVERSE REACTIONS

Dose-limiting toxicities are myelosuppression and cardiotoxicity (see **WARNINGS AND PRECAUTIONS** section).

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 hydrochloride injection administration. Local toxicity, rash/itch and skin changes may also occur.

**Gastrointestinal:** Acute nausea and vomiting occur frequently in most patients. This may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) has been reported to occur 5 to 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 hydrochloride is extravasated during administration (see **DOSE AND ADMINISTRATION** section). 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** section).

**Hematological:** A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) are the predominant manifestations of epirubicin bone marrow/hematologic 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 (e.g., peripheral blood progenitor cells and/or colony-stimulating factors) may be required. Thrombocytopenia and anemia 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** section.

**Body as a Whole:** Phlebitis, fever and malaise/asthenia have been reported following administration of epirubicin hydrochloride.

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.

**Ocular:** conjunctivitis, keratitis.

**Other:** infection, acute lymphocytic leukemia, acute myelogenous leukemia.

#### Clinical Trial Adverse Drug Reactions

##### 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** section of the full Product Monograph] 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.

Event	% of Patients					
	FEC-100/CEF-120 (N = 620)		FEC-50 (N = 280)		CMF (N = 360)	
	Grades 1 to 4	Grades 3/4	Grades 1 to 4	Grades 3/4	Grades 1 to 4	Grades 3/4
<b>Hematologic</b>						
Leukopenia	80.3	58.6	49.6	1.5	98.1	60.3
Neutropenia	80.3	67.2	53.9	10.5	95.8	78.1
Anemia	72.2	5.8	12.9	0	70.9	0.9
Thrombocytopenia	48.8	5.4	4.6	0	51.4	3.6
<b>Endocrine</b>						
Amenorrhea	71.8	0	69.3	0	67.7	0
Hot flashes	38.9	4.0	5.4	0	69.1	6.4
<b>Body as a Whole</b>						
Lethargy	45.8	1.9	1.1	0	72.7	0.3
Fever	5.2	0	1.4	0	4.5	0
<b>Gastrointestinal</b>						
Nausea/vomiting	92.4	25.0	83.2	22.1	85.0	6.4
Mucositis	58.5	8.9	9.3	0	52.9	1.9
Diarrhea	24.8	0.8	7.1	0	50.7	2.8
Anorexia	2.9	0	1.8	0	5.8	0.3
<b>Infection</b>						
Infection	21.5	1.6	15.0	0	25.9	0.6
Febrile neutropenia	NA	6.1	0	0	NA	1.1
<b>Ocular</b>						
Conjunctivitis/keratitis	14.8	0	1.1	0	38.4	0
<b>Skin</b>						
Alopecia	95.5	56.6	69.6	19.3	84.4	6.7
Local toxicity	19.5	0.3	2.5	0.4	8.1	0
Rash/itch	8.9	0.3	1.4	0	14.2	0
Skin changes	4.7	0	0.7	0	7.2	0
FEC and CEF = cyclophosphamide + epirubicin + fluorouracil CMF = cyclophosphamide + methotrexate + fluorouracil Grade 1 or 2 changes in transaminase levels were observed but were more frequently seen with CMF than with CEF. NA = not available						

#### Delayed Events

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

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

**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/hematologic and gastro-intestinal effects (see **WARNINGS AND PRECAUTIONS** section). 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** section.

##### 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 hydrochloride 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 to 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** section).

**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** section). 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<sup>2</sup> p.o. on days 1 to 14,
- epirubicin: 60 mg/m<sup>2</sup> i.v. on days 1 and 8, and
- 5-fluorouracil: 500 mg/m<sup>2</sup> i.v. on 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 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup> administered at 21-day intervals. The recommended single dose may be divided over 2 successive days. An alternative weekly dosage schedule of 12.5 mg/m<sup>2</sup> to 25 mg/m<sup>2</sup> 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<sup>2</sup>.

#### **Small Cell Lung Cancer:**

**Single Agent:** Epirubicin hydrochloride, as a single agent, can be used at 90 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup> administered every 3 weeks.

**Combination Therapy:** Epirubicin has been used in several different combinations with other antineoplastic agents at doses ranging from 50 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup>. 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, as a single agent, can be used at doses of 120 mg/m<sup>2</sup> to 150 mg/m<sup>2</sup> administered day 1, every 3 to 4 weeks.

**Combination Therapy:** Epirubicin, in combination with etoposide, cisplatin, mitomycin, vindesine and vinblastine, can be used at doses of 90 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup> administered day 1, every 3 to 4 weeks.

#### **Non-Hodgkin's Lymphoma:**

**Single Agent:** Epirubicin hydrochloride, as a single agent, can be used at doses of 75 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup> at 21-day intervals.

**Combination Therapy:** Epirubicin at doses of 60 mg/m<sup>2</sup> to 75 mg/m<sup>2</sup> 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<sup>2</sup> every 2 weeks or 70 mg/m<sup>2</sup> every 3 to 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 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup> at 3 to 4-week intervals.

**Combination Therapy:** In patients with prior therapy, epirubicin can be used in combination at doses of 50 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup> at 3 to 4-week intervals. Epirubicin at doses of 50 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup> in combination with cisplatin and cyclophosphamide can be used for initial therapy of ovarian cancer repeated at 3 to 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 mg/m<sup>2</sup> to 100 mg/m<sup>2</sup>.

**Combination Therapy:** Epirubicin, at a dose of 80 mg/m<sup>2</sup> 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 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, 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 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.

Epirubicin hydrochloride 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 **WARNINGS AND PRECAUTIONS** section). 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 with other drugs is not recommended.

Epirubicin hydrochloride 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, refer to SPECIAL HANDLING INSTRUCTIONS section.**

#### **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 to 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 anthracene 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 perinuclear chromatin binding, rapid inhibition of mitotic activity, mutagenesis and chromosomal aberrations.

Animal studies have shown activity in a wide spectrum of experimental tumors, 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-hematologic side effects such as vomiting and mucositis, than doxorubicin.

#### **Early Stage Breast Cancer Studies**

Two randomized, open-label, multi-centre studies evaluated epirubicin hydrochloride 100 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup> 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** section of the full Product Monograph for complete study descriptions and overall results; see **ADVERSE REACTIONS** section.)

Study MA.5 evaluated 120 mg/m<sup>2</sup> 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<sup>2</sup> doses of epirubicin per course in combination with fluorouracil and cyclophosphamide (FEC-100) or lower-dose FEC-50 in pre- and postmenopausal 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 to 3 positive nodes, yet CEF-120 still produced overall advantages in relapse free survival (RFS) and overall survival (OS) (see below and refer to the **CLINICAL TRIALS** section of the full Product Monograph). 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** section of the full Product Monograph). 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 to 40 hours in humans. Urinary excretion accounts for approximately 9% to 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°C to 8°C), protected from light, and retained in original carton until time of use. 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 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<sup>1</sup>. 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 decolorize 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.

### Needles, syringes, disposable and non-disposable equipment:

Rinse equipment with an appropriate quantity of sodium hypochlorite solution. Discard the solution in the sewer system with running water and discard 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 5 mL, 25 mL and 100 mL glass vials, each vial containing 2 mg/mL of epirubicin hydrochloride.

The 5 mL vials are packaged and supplied in single vial cartons.

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.

CP124505	5 mL Vials – Each mL contains 2 mg of Epirubicin Hydrochloride Ph. Eur., 9 mg of Sodium Chloride USP, Water for Injection USP, q.s. and Hydrochloric Acid NF, q.s. for pH adjustment.
CP124525	25 mL Vials – Each mL contains 2 mg of Epirubicin Hydrochloride Ph. Eur., 9 mg of Sodium Chloride USP, Water for Injection USP, q.s. and Hydrochloric Acid NF, q.s. for pH adjustment.
CP1245B1	100 mL Vials – Each mL contains 2 mg of Epirubicin Hydrochloride Ph. Eur., 9 mg of Sodium Chloride USP, Water for Injection USP, q.s. and Hydrochloric Acid NF, q.s. for pH adjustment.

<sup>1</sup> Distributed by International Medication Systems of Canada, Ltd.

### PHARMACEUTICAL PARTNERS OF CANADA INC.

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