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Rev. 1

Pharmorubicin® CS

Epirubicin Hydrochloride

CDS

AfME markets using same as LPD: Ghana and Nigeria

1. NAME OF THE MEDICINAL PRODUCT

Pharmorubicin 50 mg/25 ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection containing 2 mg of epirubicin hydrochloride per milliliter (mL) of solution

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Epirubicin hydrochloride is indicated for the treatment of the following:

- transitional cell bladder cancer
- early breast cancer
- metastatic/advanced breast cancer
- gastro-esophageal cancer
- head and neck cancer
- primary hepatocellular cancer
- acute leukemia
- non-small-cell lung cancer
- small-cell lung cancer
- non-Hodgkin’s lymphoma
- Hodgkin’s lymphoma
- multiple myeloma
- ovarian cancer
- pancreatic cancer

- hormone-refractory prostatic cancer
- rectal cancer
- soft-tissue and bone sarcomas

4.2. Posology and method of administration

Epirubicin hydrochloride is usually administered by intravenous injection. Intravesical administration has been found beneficial in the treatment of superficial bladder cancer as well as in the prophylaxis of tumor recurrence after transurethral resection. The intra-arterial route of administration has also been used to produce intense local activity with reduced general toxicity (see Section 4.4).

Intravenous (IV) Administration

The total epirubicin hydrochloride dose per cycle may differ according to its use within a specific treatment regimen (e.g., given as a single agent or in combination with other cytotoxic drugs) and according to the indication.

Epirubicin hydrochloride should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose solution). 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. 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 Section 4.4).

Standard starting dose regimens. As a single agent, the recommended standard starting dose of epirubicin hydrochloride per cycle in adults is 60-120 mg/m^2 of body surface area. The recommended starting dose of epirubicin hydrochloride when used as a component of adjuvant therapy in patients with axillary-node positive breast cancer is 100 to 120 mg/m^2. The total starting dose per cycle may be given as a single dose or divided over 2-3 successive days. Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), each treatment cycle could be repeated every 3 to 4 weeks. If epirubicin hydrochloride is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly (see reference for specific indication).

High starting dose regimens. High starting doses of epirubicin hydrochloride may be used in the treatment of breast and lung cancer. As a single agent, the recommended high starting dose of epirubicin hydrochloride per cycle in adults (up to 135 mg/m^2) should be administered on day 1 or in divided doses on days 1, 2, 3, every 3 to 4 weeks. In combination therapy, the recommended high starting dose (up to 120 mg/m^2) should be administered on day 1, every 3 to 4 weeks.

Dose Modifications

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

Hepatic Dysfunction: Dose reductions are recommended in patients with the following serum chemistry values:

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

- Bilirubin > 3 mg/dL or AST > 4 times upper limit of normal:
  ¼ of recommended starting dose.

Other Special Populations. Lower starting doses or longer intervals between cycles may need to be considered for heavily pre-treated patients or patients with neoplastic bone marrow infiltration (see section 4.4 Special warnings and precautions for use). Standard starting doses and regimens have been used in the elderly.

Intravesical Administration

Epirubicin hydrochloride should be instilled using a catheter and retained intravesically for 1 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation. Intravesical administration is not suitable for the treatment of invasive tumors which have penetrated the muscular layer of the bladder wall.

Superficial bladder tumors

Single instillation: A single instillation of 80-100 mg immediately following transurethral resection (TUR) is recommended.

4-8 week course followed by monthly instillation: Eight weekly instillations of 50 mg (in 25-50 mL of saline solution) starting 2 to 7 days following TUR are recommended. In the case of local toxicity (chemical cystitis), the dose should be reduced to 30 mg. Patients may receive 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage.

Intra-arterial Administration

Patients with hepatocellular carcinoma may receive a bolus infusion into the main hepatic artery in doses of 60 to 90 mg/m^2 at intervals of 3 weeks to 3 months or in doses of 40 to 60 mg/m^2 in 4-week cycles.

4.3. Contraindications

Hypersensitivity to epirubicin or any other component of the product, other anthracyclines or anthracenediones.

Intravenous use:

- persistent myelosuppression
- severe hepatic impairment
- myocardiopathy
- recent myocardial infarction
- severe arrhythmias
- previous treatments with maximum cumulative doses of epirubicin hydrochloride and/or other anthracyclines and anthracenediones (see Section 4.4)

Intravesical use:

- urinary tract infections
- inflammation of the bladder
- hematuria

4.4. Special warnings and precautions for use

General

Epirubicin should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy.

Patients should recover from acute toxicities (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin hydrochloride (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 epirubicin hydrochloride does require special attention for possible clinical complications due to profound myelosuppression.

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 electrocardiogram (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.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin hydrochloride in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution (see Section 5.1).

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.

Given the risk of cardiomyopathy, a cumulative dose of 900 mg/m^2 epirubicin hydrochloride should be exceeded only with extreme caution.

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 (e.g., trastuzumab). Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see Section 4.5). 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 variable. Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months 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. However, cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.

There have been sporadic reports of fetal/neonatal cardiotoxic events including fetal death following in utero exposure to epirubicin (see Section 4.6).

It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

Hematologic Toxicity

As with other cytotoxic agents, epirubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. 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

Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These leukemias can have a 1- to 3-year latency period. (see Section 5.1).

Gastrointestinal

Epirubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Liver Function

The major route of elimination of epirubicin 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 Sections 4.2 and 5.2). Patients with severe hepatic impairment should not receive epirubicin (see Section 4.3).

Renal Function

Serum creatinine should be assessed before and during therapy. Dosage adjustment is necessary in patients with serum creatinine >5 mg/dL (see Section 4.2).

Effects at Site of Injection

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see Section 4.2).

Extravasation

Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately stopped.

Other

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.

Tumor-Lysis Syndrome

Epirubicin may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

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.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route - Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, hematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., uretheral obstruction due to massive intravesical tumors).

Intra-arterial route - Intra-arterial administration of epirubicin (transcatheter arterial embolization for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed

following intravenous administration of epirubicin) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Embryo-fetal toxicity

Epirubicin can cause genotoxicity. An effective method of contraception is required for both male and female patients during and for a period after treatment with epirubicin (see Section.6). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

4.5. Interaction with other medicinal products and other forms of interaction

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 Section 4.4). 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.

Epirubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect epirubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity (see Section 4.4).

Cimetidine increased the AUC of epirubicin by 50% and should be stopped during treatment with epirubicin.

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites, the latter being, however, neither toxic nor active. Coadministration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.

4.6. Fertility, pregnancy and lactation

(See Section 5.3 Preclinical safety data)

Impairment of Fertility

Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Pregnancy

Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and to use effective contraceptive methods during treatment and for at least 6.5 months after last dose.

There are no studies in pregnant women. Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman. Avoid the use of epirubicin during the 1st trimester. Available human data do not establish the presence or absence of major birth defects and miscarriage related to the use of epirubicin during the 2nd and 3rd trimesters.

If epirubicin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. There have been sporadic reports of fetal and/or neonatal transient ventricular hypokinesia, transient elevation of cardiac enzymes, and of fetal death from suspected anthracycline-induced cardiotoxicity following in utero exposure to epirubicin in 2nd and/or 3rd trimesters (see Section 4.4). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.

Lactation

It is not known whether epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from epirubicin, advise lactating women not to breastfeed during treatment with epirubicin and for at least 7 days after last dose..

4.7. Effects on ability to drive and use machines

The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated.

4.8. Undesirable effects

A large number of clinical trials with epirubicin, administered at both conventional and high doses in different indications, have been conducted. Serious drug-related adverse events that occurred during clinical trials are listed below. Data from post-marketing surveillance are also included.

Table 1: Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reactions
Infections and infestations	Sepsis*

System Organ Class	Adverse Drug Reactions
	Pneumonia*
	Conjunctivitis
	Infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Acute myeloid leukaemia
	Acute lymphocytic leukaemia
Blood and lymphatic system disorders	Febrile neutropenia
	Leukopenia
	Neutropenia
	Thrombocytopenia
	Anaemia
Immune system disorders	Anaphylactic reaction*
Metabolism and nutrition disorders	Dehydration*
	Hyperuricaemia*
	Decreased appetite
Eye disorders	Keratitis
Cardiac disorders	Cardiac failure congestive
	Ventricular tachycardia
	Atrioventricular block
	Bundle branch block
	Bradycardia
Vascular disorders	Shock*
	Haemorrhage*
	Embolism arterial*
	Embolism
	Thrombophlebitis*
	Phlebitis*
	Hot flush
	Flushing*
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism*
Gastrointestinal disorders	Gastrointestinal haemorrhage*
	Gastrointestinal ulcer*
	Diarrhoea
	Mucosal inflammation
	Stomatitis
	Vomiting
	Gastrointestinal erosion*
	Gastrointestinal pain*
	Abdominal discomfort
	Nausea
	Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia
	Skin toxicity
	Photosensitivity reaction*
	Rash/Pruritus
	Skin disorder
	Erythema*
	Skin hyperpigmentation*

System Organ Class	Adverse Drug Reactions
	Nail pigmentation*
	Urticaria*
Renal and urinary disorders	Chromaturia*†
Reproductive system and breast disorders	Amenorrhoea
General disorders and administration site conditions	Asthenia
	Chills*
	Pyrexia*
	Malaise
Investigations	Ejection fraction decreased
	Transaminases abnormal
Injury, poisoning and procedural complications	Chemical cystitis*§
	Recall phenomenon*Δ

* ADR identified post-marketing.
† Red coloration of urine for 1 to 2 days after administration.
§ Following intravesical administration.
Δ Hypersensitivity to irradiated skin (radiation-recall reaction).

4.9. Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

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

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

Clinical Studies

Adjuvant Treatment of Patients with Early Breast Cancer

Two randomized, open-label, multicenter studies evaluated the use of epirubicin hydrochloride 100 to 120 mg/m^2 in combination with cyclophosphamide and fluorouracil for the adjuvant treatment of patients with axillary-node positive breast cancer and no evidence of distant metastatic disease (Stage II or III). Study MA-5 evaluated 120 mg/m^2 of epirubicin hydrochloride per course in combination with cyclophosphamide and fluorouracil (CEF-120 regimen). This study randomized premenopausal and perimenopausal women with one or more positive lymph nodes to an epirubicin hydrochloride -containing CEF-120 regimen or to a CMF regimen. Study GFEA-05 evaluated the use of 100 mg/m^2 of epirubicin hydrochloride per course in combination with fluorouracil and cyclophosphamide (FEC-100). This study randomized pre- and postmenopausal women to the FEC-100 regimen or to a lower-dose FEC-50 regimen. In the GFEA-05 study, eligible patients were either required to have ≥4 nodes involved with tumor or, if only 1 to 3 nodes were positive, to have negative estrogen- and progesterone-receptors and a histologic tumor grade of 2 or 3. A total of 1281 women participated in these studies. Patients with T4 tumors were not eligible for either study.

Table 2 shows the treatment regimens that the patients received. The primary endpoint of the trials was relapse-free survival, i.e., time to occurrence of a local, regional, or distant recurrence, or disease-related death. Patients with contralateral breast cancer, second primary malignancy or death from causes other than breast cancer were censored at the time of the last visit prior to these events.

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

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

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

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

The efficacy endpoints of relapse-free survival (RFS) and overall survival (OS) were analyzed using Kaplan-Meier methods in the intent-to-treat (ITT) patient populations in each study. Results for endpoints were initially analyzed after up to 5 years of follow-up and these results are presented in the text below and in Table 3. Results after up to 10 years of follow-up are presented in Table 3. In Study MA-5, epirubicin hydrochloride -containing combination therapy (CEF-120) showed significantly longer RFS than CMF (5-year estimates were 62% versus 53%, stratified logrank for the overall RFS p = 0.013). The estimated reduction in the risk of relapse was 24% at 5 years. The OS was also greater for the epirubicin hydrochloride -containing CEF-120 regimen than for the CMF regimen (5-year estimate 77% versus 70%; stratified logrank for overall survival p = 0.043; non-stratified logrank p = 0.13). The estimated reduction in the risk of death was 29% at 5 years.

In Study GFEA-05, patients treated with the higher-dose epirubicin hydrochloride regimen (FEC-100) had a significantly longer 5-year RFS (estimated 65% versus 52%, logrank for the overall RFS p = 0.007) and OS (estimated 76% versus 65%, logrank for the overall survival p = 0.007) than patients given the lower dose regimen (FEC-50). The estimated reduction in risk of relapse was 32% at 5 years. The estimated reduction in the risk of death was 31% at 5 years.

Results of follow-up up to 10 years (median follow-up = 8.8 years and 8.3 years, respectively for Study MA-5 and Study GFEA-05) are presented in Table 3.

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

Table 3. Efficacy Results from Phase 3 Studies of Patients with Early Breast Cancer*

	MA-5 Study		GFEA-05 Study	
	CEF-120 N=356	CMF N=360	FEC-100 N=276	FEC-50 N=289
RFS at 5 yrs (%)	62	53	65	52
Hazard ratio†	0.76		0.68	
2-sided 95% CI	(0.60, 0.96)		(0.52, 0.89)	
Log-rank Test stratified**	(p = 0.013)		(p = 0.007)	
OS at 5 yrs (%)	77	70	76	65
Hazard ratio†	0.71		0.69	
2-sided 95% CI	(0.52, 0.98)		(0.51, 0.92)	
Log-rank Test stratified**	(p = 0.043) (unstratified p = 0.13)		(p = 0.007)	

	MA-5 Study		GFEA-05 Study	
	CEF-120 N=356	CMF N=360	FEC-100 N=276	FEC-50 N=289
RFS at 10 yrs (%)	51	44	49	43
Hazard ratio†	0.78		0.78	
2-sided 95% CI	(0.63, 0.95)		(0.62, 0.99)	
Log-rank Test stratified**	(p = 0.017) (unstratified p = 0.023)		(p = 0.040) (unstratified p = 0.09)	
OS at 10 yrs (%)	61	57	56	50
Hazard ratio†	0.82		0.75	
2-sided 95% CI	(0.65, 1.04)		(0.58, 0.96)	
Log-rank Test stratified**	(p = 0.100) (unstratified p = 0.18)		(p = 0.023) (unstratified p = 0.039)	

*Based on Kaplan-Meier estimates

**Patients in MA-5 were stratified by nodal status (1-3, 4-10, and >10 positive nodes), type of initial surgery (lumpectomy versus mastectomy), and by hormone receptor status (ER or PR positive (≥10 fmol), both negative (<10 fmol), or unknown status). Patients in GFEA-05 were stratified by nodal status (1-3, 4-10, and >10 positive nodes).

†Hazard ratio: CMF:CEF-120 in MA-5, FEC-50:FEC-100 in GFEA-05

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

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

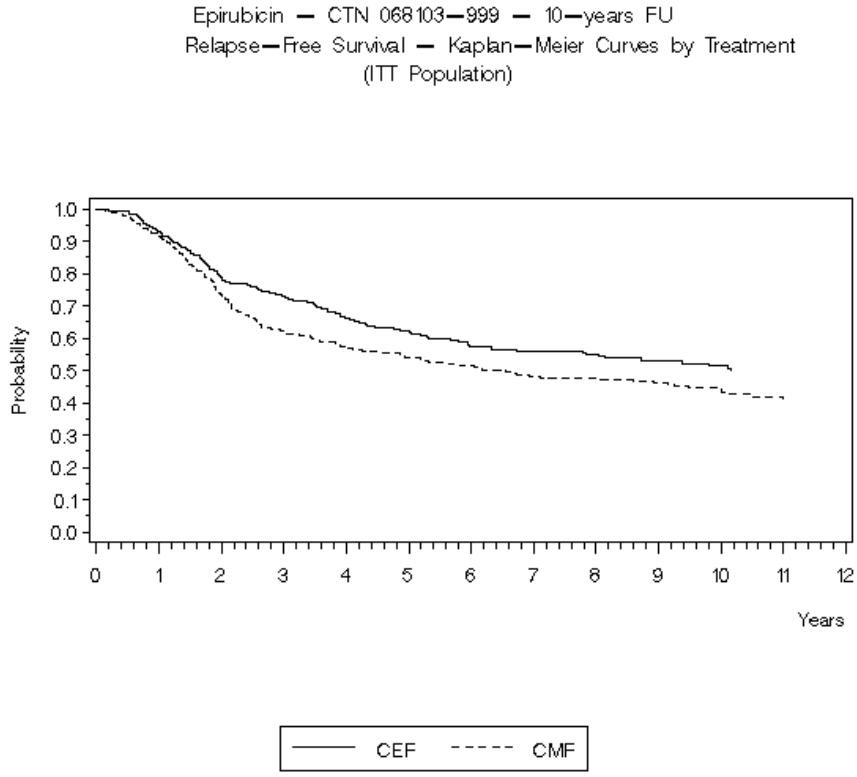


Figure 2. Overall Survival in Study MA-5

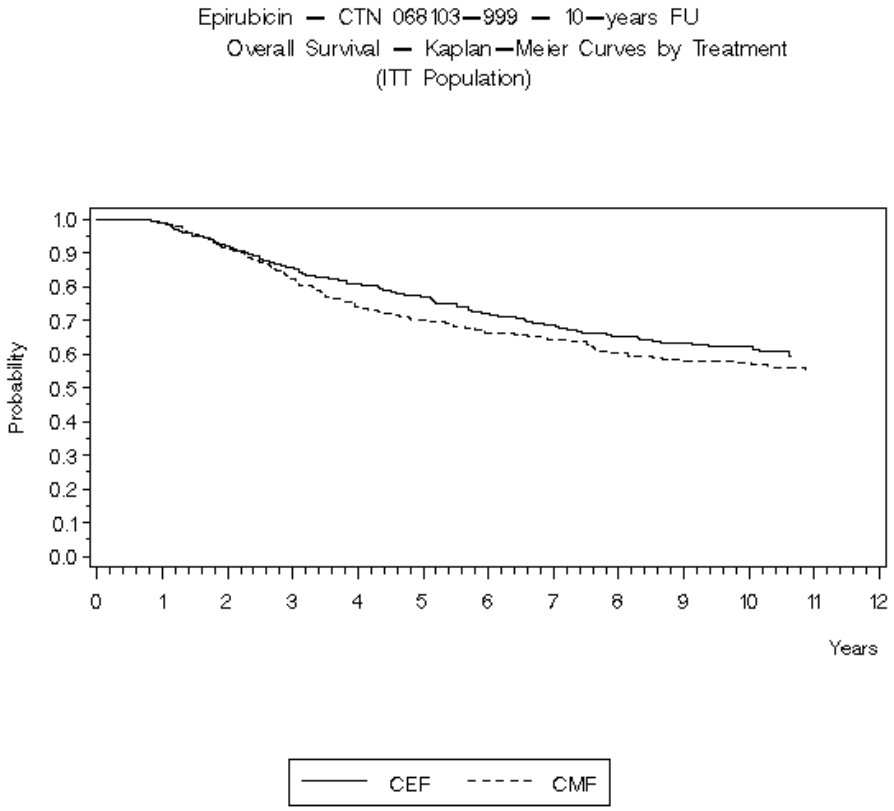


Figure 3. Relapse-Free Survival in Study GFEA-05

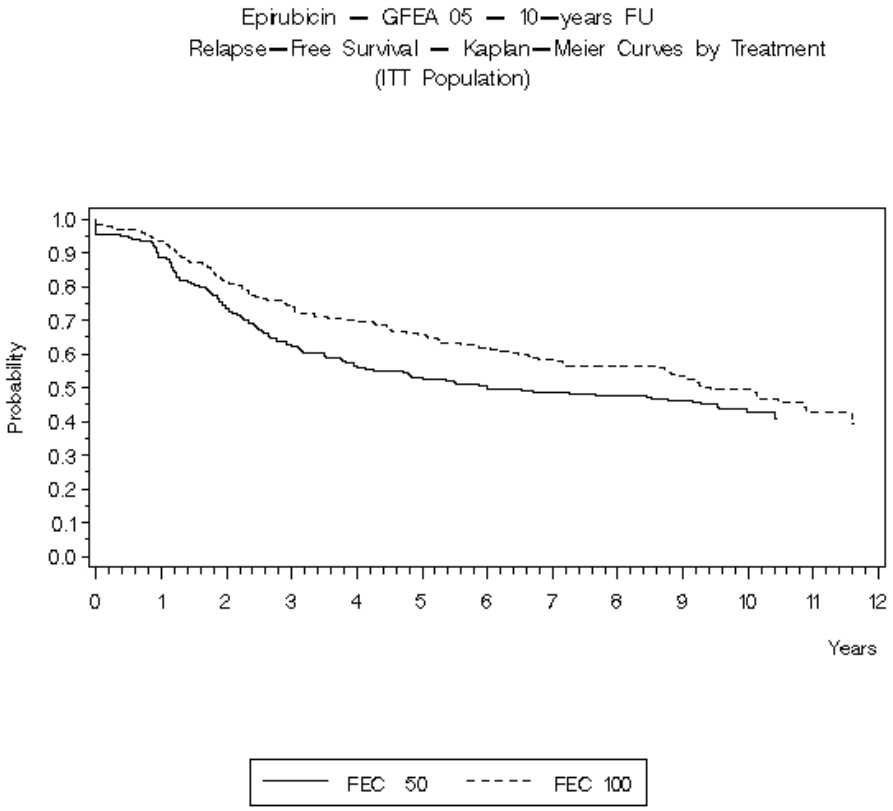
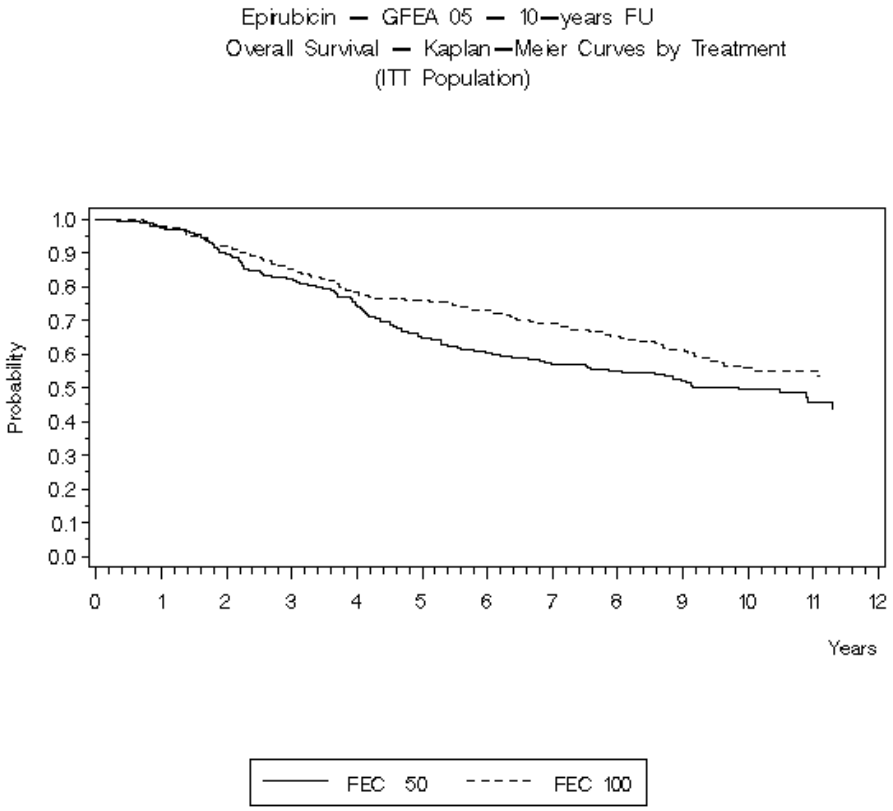


Figure 4. Overall Survival in Study GFEA-05

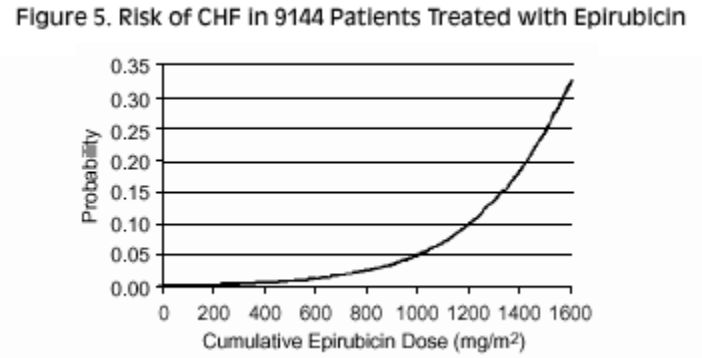


See Table 3 for statistics on 5 and 10 year analyses.

Cardiac Function

In a retrospective survey, including 9144 patients, mostly with solid tumors in advanced stages, the probability of developing CHF increased with increasing cumulative doses of epirubicin hydrochloride (Figure 5). The estimated risk of epirubicin hydrochloride -treated patients developing clinically evident CHF was 0.9% at a cumulative dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. In the adjuvant treatment of breast cancer, the maximum cumulative dose used in clinical trials was 720 mg/m^2. The risk of developing CHF in the absence of other cardiac risk factors increased steeply after an epirubicin hydrochloride cumulative dose of 900 mg/m^2.

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

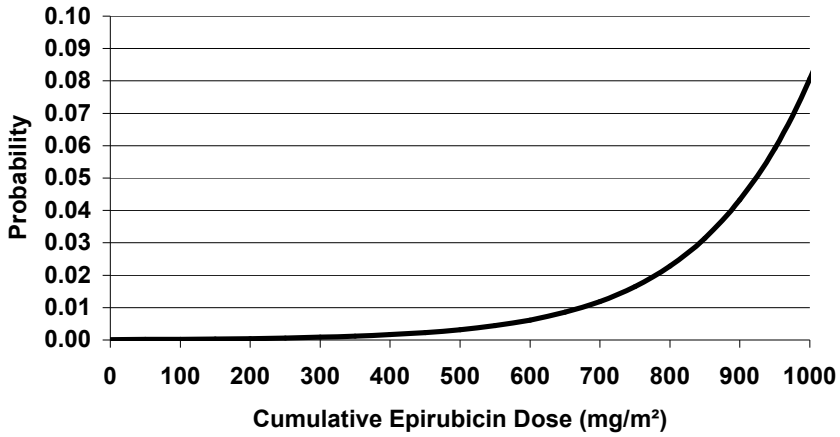


In another retrospective survey of 469 epirubicin hydrochloride -treated patients with metastatic or early breast cancer, the reported risk of CHF was comparable to that observed in the larger study of over 9000 patients.

Secondary Leukemia

An analysis of 7110 patients who received adjuvant treatment with epirubicin hydrochloride in controlled clinical trials as a component of poly-chemotherapy regimens for early breast cancer, showed a cumulative risk of secondary acute myelogenous leukemia or myelodysplastic syndrome (AML/MDS) of about 0.27% (approximate 95% CI, 0.14-0.40) at 3 years, 0.46% (approximate 95% CI, 0.28-0.65) at 5 years and 0.55% (approximate 95% CI, 0.33-0.78) at 8 years. The risk of developing AML/MDS increased with increasing epirubicin hydrochloride cumulative doses as shown in Figure 6.

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



AML/MDS rates increased with epirubicin hydrochloride dose per cycle, and cumulative dose. For instance, in the MA-5 trial, in patients that received intensive doses of epirubicin

hydrochloride (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.

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

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

Years from Treatment Start	Cumulative Probability of Developing AML/MDS % (95% CI)			
	Cyclophosphamide Cumulative Dose ≤6,300 mg/m^2		Cyclophosphamide Cumulative Dose >6,300 mg/m^2	
	Epirubicin hydrochloride Cumulative Dose ≤720 mg/m^2 N=4760	Epirubicin hydrochloride Cumulative Dose >720 mg/m^2 N=111	Epirubicin hydrochloride Cumulative Dose ≤720 mg/m^2 N=890	Epirubicin hydrochloride Cumulative Dose >720 mg/m^2 N=261
3	0.12 (0.01-0.22)	0.00 (0.00-0.00)	0.12 (0.00-0.37)	4.37 (1.69-7.05)
5	0.25 (0.08-0.42)	2. 38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)
8	0.37 (0.13-0.61)	2. 38 (0.00-6.99)	0.31 (0.00-0.75)	4.97 (2.06-7.87)

5.2. Pharmacokinetic properties

Epirubicin hydrochloride pharmacokinetics are linear over the dose range of 60 to 150 mg/m^2 and plasma clearance is not affected by the duration of infusion or administration schedule.

Distribution

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

Metabolism

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

1) reduction of the C-13 keto-group with the formation of the 13(S)-dihydro derivative, epirubicinol;

2) conjugation of both the unchanged drug and epirubicinol with glucuronic acid;

3) loss of the amino sugar moiety through a hydrolytic process with the formation of the doxorubicin and doxorubicinol aglycones; and

4) loss of the amino sugar moiety through a redox process with the formation of the 7-deoxy-doxorubicin aglycone and 7-deoxy-doxorubicinol aglycone. Epirubicinol has in vitro cytotoxic activity one-tenth that of epirubicin. As plasma levels of epirubicinol are lower than those of the unchanged drug, they are unlikely to reach in vivo concentrations sufficient for cytotoxicity. No significant activity or toxicity has been reported for the other metabolites.

Excretion

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

Pharmacokinetics in Special Populations

Hepatic Impairment. Epirubicin is eliminated by both hepatic metabolism and biliary excretion and clearance is reduced in patients with hepatic dysfunction. In a study of the effect of hepatic dysfunction, patients with solid tumors were classified into 3 groups. Patients in Group 1 (n = 22) had serum AST (SGOT) levels above the upper limit of normal (median: 93 IU/L) and normal serum bilirubin levels (median: 0.5 mg/dL) and were given epirubicin hydrochloride doses of 12.5 to 90 mg/m^2. Patients in Group 2 had alterations in both serum AST (median: 175 IU/L) and bilirubin levels (median: 2.7 mg/dL) and were treated with an epirubicin hydrochloride dose of 25 mg/m^2 (n = 8). Their pharmacokinetics were compared to those of patients with normal serum AST and bilirubin values, who received epirubicin hydrochloride doses of 12.5 to 120 mg/m^2. The median plasma clearance of epirubicin hydrochloride was decreased compared to patients with normal hepatic function by about 30% in patients in Group 1 and by 50% in patients in Group 2. Patients with more severe hepatic impairment have not been evaluated (see Sections 4.2 and 4.4).

Renal Impairment. No significant alterations in the pharmacokinetics of epirubicin hydrochloride or its major metabolite, epirubicinol, have been observed in patients with serum creatinine <5 mg/dL. A 50% reduction in plasma clearance was reported in four patients with serum creatinine ≥5 mg/dL (see Sections 4.2 and 4.4). Patients on dialysis have not been studied.

5.3. Preclinical safety data

Epirubicin is mutagenic, clastogenic, and carcinogenic in animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium Chloride
Hydrochloric acid
Water for Injections

6.2. Incompatibilities

Epirubicin 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 epirubicin. Epirubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

6.3. Shelf life

Keep out of the sight and reach of children.

Do not use Pharmorubicin after the expiry date which is stated on the Carton/Vial label after EXP:. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.4. Special precautions for storage

Pharmorubicin injection presented in plastic CYTOSAFE® vials. Store at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light.

Ready-to-use solution for injection

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15 - 25°C).

6.5. Nature and contents of container

CYTOSAFE® vials containing 50 mg of epirubicin hydrochloride (strength 2 mg/mL) as a ready-to-use solution.

Pack size is 25 mL.

6.6. Special precautions for disposal and other handling

Protective measures

The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good technique for reconstitution and handling;
- Pregnant staff should be excluded from working with this drug;
- Personnel handling epirubicin should wear protective clothing: goggles, gowns, disposable gloves and masks;

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

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

- Spillage or leakage should be treated with dilute sodium hypochloride (1% available chlorine) solution, preferably by soaking, and then water;

- All cleaning materials should be disposed of as indicated previously;

- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush.

- 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. Then seek medical evaluation by a physician.

- Always wash hands after removing gloves.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. FURTHER INFORMATION

MANUFACTURED BY

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8. PRESCRIPTION STATUS

Prescription only Medicine

9. DATE OF REVISION OF THE TEXT

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