PHARMORUBICIN® CS
(epirubicin hydrochloride)

1. NAME OF THE MEDICINE

Epirubicin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Pharmorubicin contains 10 mg/5 mL and 50 mg/25 mL of epirubicin hydrochloride (strength 2 mg/mL).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection

Pharmorubicin is a clear, red ready for use solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pharmorubicin has produced responses in a wide spectrum of neoplastic diseases, and is indicated for the treatment of:
- breast cancer;
- gastric cancer;
- ovarian cancer;
- small cell lung cancer;
- lymphoma (non-Hodgkin's lymphoma);
- advanced/metastatic soft tissue sarcoma;
- superficial bladder cancer (Tis; Ta).

In bladder cancer, Pharmorubicin is also indicated in the prophylaxis of recurrence after transurethral resection of stage T1 papillary cancers and stage Ta multifocal papillary cancers (Grade 2 and 3).

4.2 Dose and method of administration

Dosage

NOTE: The recommended lifetime cumulative dose limit of Pharmorubicin is 900 mg/m^2 body surface area.

Intravenous Administration

Under conditions of normal recovery from drug-induced toxicity (particularly bone marrow depression and stomatitis), the recommended dosage schedule in adults, as described below, is as a single intravenous injection administered at 21 day intervals.

Standard doses are 75 to 90 mg/m^2. Pharmorubicin produces predominantly haematological dose limiting toxicities which are predicted from the known dose–response profile of the drug. Based on the patient's haematological status the physician should determine the choice of dose.

Higher doses, up to 135 mg/m^2 as a single agent and 120 mg/m^2 in combination, every 3-4 weeks have been effective in the treatment of breast cancer. In the adjuvant treatment of early breast cancer patients with positive lymph nodes, doses ranging from 100 mg/m^2 to 120 mg/m^2 every 3-4 weeks are recommended. Careful monitoring in regards to increased myelosuppression, nausea, vomiting and mucositis are recommended in this high dose setting.

Consideration should be given to the administration of lower starting doses (not exceeding 75-90 mg/m^2) for heavily pre-treated patients, patients with pre-existing bone marrow depression or in the presence of neoplastic bone marrow infiltration. If Pharmorubicin is used in combination with other cytotoxic drugs with potentially overlapping toxicities, the recommended dose per cycle should be reduced accordingly.

Intravesical Administration

For the treatment of papillary transitional cell carcinoma of the bladder, a therapy of 8 weekly instillations of 50 mg is recommended.

In the case of local toxicity (chemical cystitis) a dose reduction up to 30 mg is advised. For carcinoma *in-situ*, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg.

For prophylaxis of recurrences after transurethral resection of superficial tumours, 4 weekly administrations of 50 mg followed by 11 monthly instillations at the same dosage are recommended.

To avoid undue dilution with the urine, the patient should be instructed not to drink any fluid in the twelve hours prior to instillation.

Intravesical administration is not suitable for the treatment of invasive tumours which have penetrated the muscular layer of the bladder wall.

Preparation of Solution (see Section 4.4 Special warnings and precautions for use)

Pharmorubicin can be used in combination with other anti-tumour agents, but it is not recommended that it be mixed with these drugs in the same container (also see Section 6.2 Incompatibilities).

Storage of the Pharmorubicin ready-to-use 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 room temperature (15ºC-25ºC).

Pharmorubicin contains no antimicrobial preservative. Pharmorubicin are single use only vials and any unused portion must be discarded after use. From a microbiological point of view, the products should be used immediately after first penetration of the rubber stopper.

Compatibility
Pharmorubicin is compatible with the following infusion media:
- 0.9% Sodium chloride
- 5% Glucose
- 0.9% Sodium chloride with 5% glucose

Pharmaceutical Precautions

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 Pharmorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow containment 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 hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.

All cleaning materials should be disposed of as indicated previously.

Accidental contact with the eyes or skin should be treated immediately. Copious lavage with water is appropriate treatment for contact with the eyes, whereas water or soap and water, or sodium bicarbonate solution may be used on the skin; medical attention should be sought.

Method of Administration

Pharmorubicin is intended for intravenous or intravesical administration only. It must not be administered by the intramuscular, subcutaneous or oral routes.

Intravenous Administration

Care in the intravenous administration of Pharmorubicin will reduce the chance of perivenous infiltration (see Section 4.4 Special warnings and precautions for use, Extravasation). It may also decrease the chance of local reactions, such as urticaria and erythematous streaking.

It is recommended that Pharmorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Glucose Injection USP. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. To minimise the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration

and the infusion should be immediately terminated and restarted in another vein (see Section 4.4 Special warnings and precautions for use, *Extravasation*).

Intravesical Administration

Pharmorubicin, to be instilled using a catheter, should be retained intravesically for 1 hour. The patient should be instructed to void at the end of this time. During instillation, the pelvis of the patient should be rotated to ensure extensive contact of the solution with the vesical mucosa.

Dosage Adjustment

Renal Impairment: 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 Impairment: As clinical toxicity may be increased by the presence of impaired liver function, Pharmorubicin dosage must be reduced if hepatic function is impaired, according to the following table:

Serum Bilirubin Levels	Recommended Dose
20 – 50 µmol/L	1/2 normal dose
Over 50 µmol/L	1/4 normal dose

Other Special Populations: Haematological toxicity may require dose reduction, delay or suspension of Pharmorubicin therapy. Lower doses may be necessary if Pharmorubicin is used concurrently with other anti-neoplastic agents.

4.3 Contraindications

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

Situations in which patients should not be treated with intravenous Pharmorubicin are:

- persisting myelosuppression or severe stomatitis induced by previous drug therapy or radiotherapy;
- presence of generalised infections;
- marked liver function impairment;
- previous history of, or in the presence of, cardiac impairment (severe arrhythmias and cardiomyopathy, previous myocardial infarction);
- unstable angina pectoris;
- previous treatments with maximum cumulative doses of mitoxantrone, mitomycin C or other anthracyclines, such as doxorubicin or daunorubicin;
- pregnancy and lactation.

Contraindications for intravesical use are:

- invasive tumours that have penetrated the bladder wall;
- urinary infections;
- inflammation of the bladder;

- catheterisation problems;
- haematuria.

4.4 Special warnings and precautions for use

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

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

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

Initial treatment with Pharmorubicin requires close observation of the patient and extensive laboratory monitoring including assessment of cardiac function (see Section 4.4 Special warnings and precautions for use, *Cardiac Function*). During each cycle of treatment patients must be carefully and frequently monitored. A blood count, renal and liver function tests should be carried out prior to each Pharmorubicin treatment.

Warnings

PHARMORUBICIN SOLUTION FOR INJECTION MUST BE HANDLED WITH CARE. IF THE SOLUTION COMES IN CONTACT WITH THE SKIN OR MUCOSAE, THE APPROPRIATE AREAS SHOULD BE WASHED IMMEDIATELY AND THOROUGHLY WITH SOAP AND WATER OR SODIUM BICARBONATE SOLUTION.

The rate of administration is dependent on the size of the vein and the dosage. It is important that the dose be administered in not less than 3 to 4 minutes. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Severe local tissue necrosis will occur if there is extravasation during administration. Venous sclerosis may result from injection into a small vessel or from repeated injections into the same vein.

Pharmorubicin must not be given by the intramuscular or subcutaneous route.

Pharmorubicin is not an antimicrobial agent.

Haematologic Toxicity

As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leukopaenia and/or granulocytopaenia (neutropaenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopaenia and neutropaenia 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. Thrombocytopaenia and anaemia may also occur.

Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone marrow infiltration by tumour or impaired liver function (when appropriate dosage reduction has not been adopted) (see Section 4.2 Dose and method of administration, Dosage Adjustment, *Other Special Populations*).

Secondary Leukaemia

Secondary leukaemia, with or without a pre-leukaemic phase, has been reported in patients treated with anthracyclines including epirubicin. Secondary leukaemia 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 leukaemias can have a 1- to 3-year latency period.

Cardiac Function

Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events. The cardiac abnormalities caused by treatment can be separated into 2 categories:

(i) ECG alterations and
(ii) Congestive heart failure (CHF).

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. ECG changes following Pharmorubicin treatment occur in about 10% of patients. 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 Pharmorubicin or within 2 to 3 months after treatment termination, but later events several months to years after completion of treatment have also been reported. Cardiomyopathy induced by anthracyclines is associated with persistent QRS voltage reduction, prolongation beyond normal limits of the systolic time interval (PEP/LVET) and a reduction of the ejection fraction and/or signs and symptoms of CHF such as dyspnoea, pulmonary oedema, dependent

oedema, 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. Pericardial effusion has also been described.

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

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of left ventricular ejection fraction (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.

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, concomitant or previous radiation of the mediastinal-pericardial area, hypertensive cardiomyopathy, previous therapy with other anthracyclines or anthracenediones, concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic agents (e.g., trastuzumab, high dose cyclophosphamide or 5-fluorouracil). 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 Interactions with other medicines and other forms of interactions). 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 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 Fertility, pregnancy and lactation).

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

Gastrointestinal

Epirubicin is emetogenic. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy.

Mucositis/stomatitis occurs frequently and generally appears early after drug administration, most commonly developing 5 to 10 days after treatment. It is painful and typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and, if severe, may progress over a few days to mucosal ulcerations with a risk of secondary infection. Most patients recover from this adverse event by the third week of therapy.

Use in Hepatic Impairment

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 Pharmorubicin. 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 Section 4.2 Dose and method of administration). Patients with severe hepatic impairment should not receive Pharmorubicin (see Section 4.3 Contraindications).

Use in Renal Impairment

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Pharmorubicin excreted by this route. However, 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 Dose and method of administration).

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 minimise the risk of phlebitis/thrombophlebitis at the injection site (see Section 4.2 Dose and method of administration, Intravenous Administration).

Extravasation

Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. The recommended administration procedures should be followed (see Section 4.2 Dose and method of administration, Intravenous Administration). Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately stopped.

Tumour-Lysis Syndrome

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

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 4.6 Fertility, pregnancy and lactation). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

Other

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

Pharmorubicin may enhance radiation-induced toxicity such as skin reactions and mucositis and may potentiate the toxicity of other anticancer therapies. This has to be taken into account particularly when using the drug in high doses and the availability of supportive care and facilities has to be considered before initiating high dose-intensive regimens.

Epirubicin may impart a red colour to the urine for one-two days after administration. Patients should be advised that such an event is not a cause for alarm.

Intravesical Route

Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterisation problems (e.g., ureteral obstruction due to massive intravesical tumours).

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Pharmorubicin is mainly used in combination with other cytotoxic drugs and additive toxicity may occur especially with regard to bone marrow/haematologic and gastrointestinal effects.

In addition, the concomitant use of Pharmorubicin with other antitumour drugs which have been reported as potentially cardiotoxic (e.g., 5-fluorouracil, cyclophosphamide, cisplatin,

taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires a close monitoring of cardiac function throughout treatment.

Concurrent administration of Pharmorubicin and propranolol may result in an additive cardiotoxic effect.

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

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.

Concurrent mediastinal radiotherapy and Pharmorubicin may be associated with enhanced myocardial toxicity of Pharmorubicin.

Pharmorubicin is extensively metabolised by the liver. Changes in hepatic function induced by concomitant therapies may affect Pharmorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Although no studies have been conducted with Pharmorubicin, it may be expected, like doxorubicin, to cause infertility during the period of drug administration. In women, Pharmorubicin may cause amenorrhoea. After termination of therapy, ovulation and menstruation may be expected to return in a few months, often accompanied by normal fertility. Premature menopause may also occur.

In male patients, oligospermia or azoospermia may be permanent, although fertility may return several years after ceasing therapy. Given the mutagenic potential of Pharmorubicin, the drug could induce chromosomal damage in human spermatozoa; therefore, males undergoing Pharmorubicin treatment should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.

Use in Pregnancy - Category D

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 is no specific information available at present concerning the use of Pharmorubicin in human pregnancy. However, as it has been shown to be embryotoxic and fetotoxic in animals, it should not be used in patients who are pregnant or are likely to become pregnant.

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 Special warnings and precautions for use). Monitor the fetus and/or neonate for cardiotoxicity and perform testing consistent with community standards of care.

Use in Lactation

It is likely that Pharmorubicin is excreted in breast milk, therefore, it is not recommended for nursing mothers unless the expected benefit outweighs any potential risk. Because of the potential for serious adverse reactions in nursing infants from epirubicin, lactating women should be advised 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 effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Dose limiting toxicities are myelosuppression and cardiotoxicity (see Section 4.4 Special warnings and precautions for use).

Drug-related adverse events that occurred during clinical trials are listed below.

More Common Reactions (>5%):

Blood and lymphatic system disorders:

Myelosuppression, leukopaenia, neutropaenia, febrile neutropaenia, thrombocytopaenia, mild anaemia, secondary infection.

Cardiac disorders:

Transient ECG changes, including low QRS voltage, tachycardia, arrhythmias, T wave flattening, ST depression and T inversion.

Gastrointestinal disorders:

Nausea, vomiting, diarrhoea, mucositis (erythema, erosions/ulcerations, bleeding). Mucositis may appear 5–10 days after the start of treatment and usually involves stomatitis with areas of painful erosions, mainly along the sides of the tongue and on the sublingual mucosa.

Skin and subcutaneous tissue disorders:

Alopecia, including the interruption of beard growth, usually reversible, occurs in 60%–90% of treated cases.

General disorders and administration site conditions:

Erythematous streaking along the infused vein.

Metabolism and nutrition disorders:

Dehydration.

Less Common Reactions (<5%):

Blood and lymphatic system disorders:

Severe thrombocytopaenia, anaemia, severe myelosuppression, pancytopaenia, sepsis, septicaemia, septic shock, tissue hypoxia, haemorrhage and death.

Cardiac disorders:

Cardiomyopathy, congestive heart failure, cardiomegaly, atrioventricular and bundle branch block, tachyarrhythmias (premature ventricular contractions, ventricular tachycardia, bradycardia).

Gastrointestinal disorders:

Oesophagitis, bleeding, hyperpigmentation of oral mucosa and abdominal pain or burning sensation.

Skin and subcutaneous tissue disorders:

Local toxicity, rash/itch, transient urticaria, erythema, flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity of irradiated skin.

General disorders and administration site conditions:

Chills, fever, malaise/asthenia, vesication, local pain, severe cellulitis and skin necrosis following perivenous drug extravasation.

Eye disorders:

Conjunctivitis, keratitis.

Immune system disorders:

Anaphylaxis.

Investigations:

Asymptomatic drops in left ventricular ejection fraction, changes in transaminase levels.

Nervous system disorders:

Weakness, dizziness, confusion, depression, paraesthesia.

Metabolism and nutrition disorders:

Hyperuricaemia, anorexia.

Neoplasms benign and malignant:

Acute lymphocytic leukaemia, acute myelogenous leukaemia.

Reproductive system disorders:

Amenorrhoea, azoospermia.

Vascular disorders:

Hot flushes, shock, thromboembolism, arterial embolism, thrombophlebitis, phlebitis, venous sclerosis.

Post-marketing Experience

Infections and infestations:

Pneumonia.

Renal and urinary disorders:

Red colouration of urine for 1 to 2 days after administration.

Respiratory, thoracic and mediastinal disorders:

Pulmonary embolism.

Injury, poisoning and procedural complications:

Chemical cystitis, sometimes haemorrhagic, and bladder constriction (following intravesical administration). Dose reduction (40%) may be necessary in these cases.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

A 36-year-old man with non-Hodgkin's lymphoma received a daily 95 mg/m^2 dose of epirubicin injection for 5 consecutive days. Five days later, he developed bone marrow aplasia, grade 4 mucositis and gastrointestinal bleeding. No signs of acute cardiac toxicity were observed. He was treated with antibiotics, colony-stimulating factors and antifungal agents and recovered completely. A 63-year-old woman with breast cancer and liver metastasis received a single 320 mg/m^2 dose of epirubicin, which resulted in hyperthermia, multiple organ failure

(respiratory and renal), lactic acidosis, increased lactate dehydrogenase and anuria, and death within 24 hours of administration.

Additional instances of administration of doses higher than recommended have been reported at doses ranging from 150 to 250 mg/m^2. The observed adverse events in these patients were qualitatively similar to known toxicities of epirubicin. Most of the patients recovered with appropriate supportive care.

Very high single doses of Pharmorubicin may be expected to cause acute myocardial degeneration within 24 hours, and severe myelosuppression (mainly leukopaenia and thrombocytopaenia) within 10-14 days and also gastrointestinal toxic effects (mainly mucositis).

If an overdose occurs, supportive treatment (including antibiotic therapy, blood and platelet transfusions, colony-stimulating factors and intensive care as needed) should be provided until the recovery of toxicities. Delayed cardiac failure may occur up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

Epirubicin cannot be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

The mechanism of action of Pharmorubicin has not been fully elucidated but is probably related to its ability to bind DNA. Cell culture studies have shown cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Pharmorubicin has proved to be active on the following experimental tumours: L 1210 ascites and P388 leukaemias, sarcoma SA 180 (solid and ascitic forms), melanoma B 16, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38.

The specificity of Pharmorubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastrointestinal tract, lymphoid organs and the gonads are the main normal tissues damaged. Degenerative or functional alterations in liver and kidneys were also seen in animals dosed with Pharmorubicin.

Toxicity studies in animals have indicated that on a weight (mg per mg) basis Pharmorubicin has a better therapeutic index and less systemic and cardiac toxicity than doxorubicin.

Pharmorubicin is immunosuppressive in animals. Although there are no clinical data on the immunosuppressive effects of Pharmorubicin, effects similar to those seen with doxorubicin may be expected.

Clinical Trials

Early Breast Cancer

Data from 2 multicentre, randomised phase 3 studies support the use of Pharmorubicin 100 to 120 mg/m^2 for the adjuvant treatment of patients with axillary-node-positive breast cancer and no evidence of distant metastatic disease (Stage II or III). In one study, an intensive cyclophosphamide/epirubicin/fluorouracil (CEF-120) regimen (epirubicin given in a dose of 60 mg/m^2 on days 1 and 8) was compared with a conventional cyclophosphamide/ methotrexate/fluorouracil (CMF) regimen. A total of 716 patients were randomised, 356 to CEF and 360 to CMF. Both disease free survival and overall survival were significantly prolonged in the CEF arm at five years. Disease free survival was 62% for CEF versus 53% for CMF (p=0.01) and overall survival was 77% for CEF versus 70% for CMF (p=0.043).

In the second study, 301 patients were randomised to receive tamoxifen 20 mg/day alone for 4 years and 303 patients were randomised to receive tamoxifen for 4 years in combination with epirubicin 50 mg/m^2 on days 1 and 8 every 4 weeks for 6 cycles. Although there was no significant difference between the two arms with regard to disease free survival and overall survival, there was a trend in favour of the combined use of epirubicin and tamoxifen. Disease free survival at two years was 85.1% versus 77.9% and at five years 70.4% versus 59.5% (p=0.07). Overall survival at two years was 93% versus 92% and at five years was 78.8% versus 72.9%.

Advanced Breast Cancer

Data from 4 open-label, multicentre, phase 3 studies support the use of Pharmorubicin for the treatment of patients with locally advanced or metastatic breast cancer. In Study 1, an intensified cyclophosphamide/epirubicin/fluorouracil (CEF-100) regimen (epirubicin given in a dose of 50 mg/m^2 on days 1 and 8) was compared with a conventional CMF regimen (n=461). Studies 2 and 3 compared cyclophosphamide/epirubicin/fluorouracil regimens where only the dose of epirubicin varied. In both of these, epirubicin was given in a dose 50 mg/m^2 on day 1 and compared with either 100 mg/m^2 on day 1 (n=456) or 50 mg/m^2 on days 1 and 8 (n=164). High dose epirubicin (135 mg/m^2) was compared to conventional dose epirubicin (75 mg/m^2) in Study 4 (n=151).

The efficacy endpoints included response rate (RR), duration of response (DR), time to tumour progression (TTP), time to treatment failure (TTF) and overall survival (OS). In Study 1, the CEF-100 regimen produced a significantly higher RR, a significantly longer TTP and a significantly longer TTF than the CMF regimen. In studies 2, 3 and 4, the higher dose epirubicin-containing regimens produced a significantly greater RR than the lower dose epirubicin-containing regimens. DR and TTF were also significantly longer in Study 3 and TTP was significantly longer in Study 4 for the higher dose epirubicin regimens.

5.2 Pharmacokinetic properties

There is evidence for a dose-response and dose-toxicity relationship for epirubicin in breast cancer, and to a lesser extent for lymphoma. This relationship is steeper and therefore more evident for doses of epirubicin above 90 mg/m^2. Current data indicate that an increase in dose (for dose intensity) produces greater response rates.

Absorption/Distribution

When Pharmorubicin is administered intravesically, the systemic absorption is minimal. As with doxorubicin, Pharmorubicin may not be expected to cross the blood-brain barrier.

Elimination

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 75–90 mg/m^2 of the drug follow a triexponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. Plasma levels of the drug's main metabolite, the 13–OH derivative, are constantly somewhat lower and virtually parallel to those of the unchanged drug. Pharmorubicin is eliminated mainly through the liver; high plasma clearance values (0.9 L/min) indicate that the slow elimination of epirubicin is due to extensive tissue distribution. Urinary excretion accounts for approximately 11% of the administered dose in 48 hours. However, like doxorubicin, biliary excretion is likely to be the major excretion route. Impairment of liver function delays plasma clearance.

5.3 Preclinical safety data

Genotoxicity

Like most other anti-tumour and immunosuppressant agents, Pharmorubicin is mutagenic in animals (see Section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy).

Carcinogenicity

Pharmorubicin is carcinogenic in animals (see Section 4.6 Fertility, pregnancy and lactation, Use in pregnancy).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid,
Sodium chloride,
Water for injections.

6.2 Incompatibilities

If Pharmorubicin is used in combination with other antitumour agents, it should not be mixed with these drugs in the same container.

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.

Pharmorubicin should not be mixed with heparin as these drugs are incompatible.

6.3 Shelf life

The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at 2°C to 8°C. Refrigerate, do not freeze.

6.5 Nature and contents of container

Pharmorubicin is supplied in polypropylene vials with halobutyl stoppers and an aluminium cap with a plastic flip-off top. in packs of 1 vial.

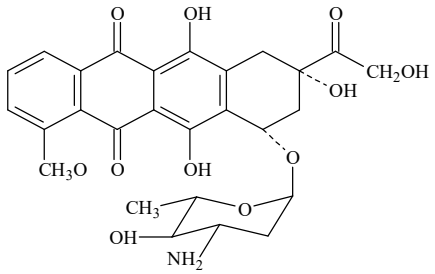
Some product strengths or pack sizes may not be available in your country.

6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Chemical Structure



.HCl

Structurally, Pharmorubicin differs from Adriamycin® (doxorubicin hydrochloride) only in the orientation of the hydroxyl group at the 4 position on the aminoglycoside ring.

The chemical name of epirubicin hydrochloride is (8S, 10S)-10-(3-Amino-2,3,6-trideoxy-α-L-*arabino*-hexopyranosyloxy)-8-glycolloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione hydrochloride.

Epirubicin hydrochloride is a red-orange, almost odourless, hygroscopic powder, sparingly soluble in water and dilute alcohol.

CAS Number

56390-09-1.

7. MANUFACTURER

Pfizer (Perth) Pty Limited
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Bentley, WA 6102
Australia

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