PRODUCT INFORMATION

EPIRUBE (epirubicin hydrochloride) Concentrated Injection
(10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL, 150mg/75mL & 200 mg/100 mL)

NAME OF THE MEDICINE

Epirubicin hydrochloride

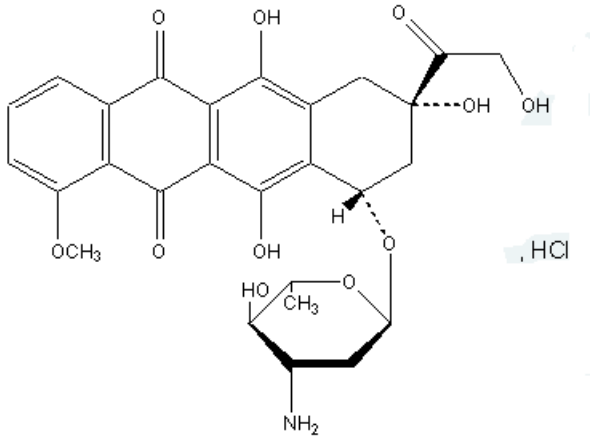
Chemical name:
(8*S*, 10*S*)-10 -(3-amino-2,3,6 -trideoxy- α-L-arabino -hexopyranosyloxy)-8 -glycolloyl-7,8,9,10 -tetrahydro-6,8,11 -trihydroxy-1 -methoxynaphthacene- 5,12 -dione hydrochloride.

DESCRIPTION

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

EPIRUBE Injection also contains sodium chloride and water for injections. Hydrochloric acid is added as necessary to adjust the pH.

Structurally, epirubicin hydrochloride differs from doxorubicin hydrochloride only in the orientation of the hydroxyl group at the 4 position on the aminoglycoside ring.



CAS: 56390-09-1

PHARMACOLOGY

The mechanism of action of epirubicin hydrochloride has not been fully elucidated but is probably related to its ability to bind deoxyribonucleic acid (DNA). Cell culture studies have shown cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin hydrochloride 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 epirubicin hydrochloride 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 epirubicin hydrochloride.

Like most other antitumour and immunosuppressant agents, epirubicin hydrochloride, under experimental conditions, has mutagenic properties and is carcinogenic in laboratory animals (see Precautions, Use in Pregnancy).

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

Clinical Pharmacology

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 75 to 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. Epirubicin hydrochloride is eliminated mainly through the liver; high plasma clearance values (0.9 L/minute) 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. As with doxorubicin, epirubicin hydrochloride may not be expected to cross the blood brain barrier. When epirubicin hydrochloride is administered intravesically, the systemic absorption is minimal.

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.

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

CLINICAL TRIALS

Early breast cancer

Data from two multicenter, randomised phase III studies support the use of epirubicin hydrochloride 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 four years and 303 patients were randomised to receive tamoxifen for four years in combination with epirubicin 50 mg/ m^2 on days 1 and 8 every four weeks for six 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 was 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 four open label, multicenter, phase III studies support the use of epirubicin hydrochloride 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 of 50 mg/m^2 on day 1 and compared with either 100mg/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 TPP was significantly longer in study 4 for the higher dose epirubicin regimens.

INDICATIONS

Epirubicin hydrochloride 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, EPIRUBE 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).

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 epirubicin hydrochloride 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 myocardial insufficiency, previous myocardial infarction, unstable angina pectoris, myocardiopathy);
- previous treatments with maximum cumulative doses of mitozantrone, 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 tract infections
- bladder problems such as inflammation of the bladder large volume of residual urine or contracted bladder
- catheterisation problems;
- haematuria.

PRECAUTIONS

General

Epirubicin hydrochloride should be administered only under the supervision of qualified doctors experienced in cytotoxic therapy.

Patients should recover from acute toxicities (e.g. stomatitis, neutropenia, thrombocytopenia and generalised infections) of prior cytotoxic treatment before beginning treatment with epirubicin hydrochloride.

While treatment with high doses of epirubicin hydrochloride (e.g. $\geq$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 epirubicin hydrochloride requires special attention for possible clinical complications due to profound myelosuppression.
Initial treatment with epirubicin hydrochloride requires close observation of the patient and extensive laboratory monitoring including assessment of cardiac function (See PRECAUTIONS, *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 epirubicin hydrochloride treatment. The routine assessment of cardiac function may include electrocardiogram (ECG) and the evaluation of left ventricular ejection fraction (LVEF).

Warnings

EPIRUBE INJECTION MUST BE HANDLED WITH CARE. IF THE PREPARATION 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.
EPIRUBE is intended for use under the direction of those experienced in cytotoxic therapy. 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 three to four 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 infection into a small vessel or from repeated injections into the same vein.

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

EPIRUBE is not an antimicrobial agent.

Intravenous route

Haematological 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 neutropenia are generally more severe with high-dose schedules reaching a nadir between 10 and 14 days after administration. This is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21.

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 DOSAGE AND ADMINISTRATION, Dose Modifications, Other Special Populations).

Secondary leukaemia

Secondary leukaemia with or without a preleukaemic phase, had been reported in patients treated with topoisomerase II inhibitors, including anthracyclines, e.g. epirubicin (see "ADVERSE EFFECTS"). 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 - Anthracycline induced cardiotoxicity

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).

Patients receiving epirubicin hydrochloride should be monitored for anthracycline induced cardiotoxicity.

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 EPIRUBE 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 EPIRUBE 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 congestive heart failure (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 hydrochloride in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution.

The onset of cardiac failure may be sudden and early recognition may increase the likelihood of benefit from treatment. Heart failure has been reported even several weeks to several months after discontinuing treatment and the risk may be higher in patients with 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 fluorouracil.

In such patients a reduction of the total cumulative dose may be required and the monitoring of cardiac function must be particularly strict. The risk/ benefit of continuing epirubicin hydrochloride treatment under conditions of impaired cardiac function has to be carefully evaluated. However, cardiotoxicity with epirubicin hydrochloride may occur in lower cumulative doses whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin hydrochloride and other anthracyclines or anthracenediones is additive.

The total (cumulative) dose levels of epirubicin hydrochloride do correlate with the incidence of drug induced congestive cardiac failure (cardiomyopathy). At a cellular level the nature of epirubicin hydrochloride induced cardiac toxicity appears to be similar to that of doxorubicin. Limitation of the total lifetime dose of epirubicin hydrochloride to 900 mg/ m^2 in good risk patients reduces the likelihood of drug induced cardiomyopathy. It is suggested that an ECG be taken before treatment. Alterations of the ECG, such as flattening or inversion of the T wave, depression of the ST segment, or the onset of arrhythmias, are generally transient and reversible and need not necessarily indicate that treatment should be stopped. It is also advisable to assess cardiac function by other techniques, such as echocardiography and measurement of the ejection fraction by radionuclide angiography. The technique should be consistent throughout follow-up.

Anthracyclines including epirubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27

weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Gastrointestinal

Epirubicin is emetigenic. 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.

Liver Function

As toxicity of epirubicin hydrochloride is enhanced by impaired liver function or bile outflow, the major route of elimination being the hepatobiliary system, dosages should be reduced in patients with impaired hepatic function (see also "DOSAGE AND ADMINISTRATION"). Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin hydrochloride. Patients with severe hepatic impairment should not receive EPIRUBE (see "CONTRAINDICATIONS").

Renal Function

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin hydrochloride excreted by this route. However, serum creatinine should be assessed before and during therapy as dosage adjustment is necessary in patients with serum creatinine >5 mg/dL (see "DOSAGE AND 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 DOSAGE AND 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 DOSAGE AND 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 epiribucin, 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.

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 EPIRUBE.

EPIRUBE 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.

Like other cytotoxic drugs, EPIRUBE may induce hyperuricaemia secondary to rapid lysis of neoplastic cells. The clinician should monitor the patient's blood uric acid level and be prepared to use such supportive and pharmacological measures as this might be necessary to control this problem

Epirubicin may impart a red colour to the urine for one to 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., uretheral obstruction due to massive intravesical tumours).

Use in pregnancy (Category D)

(Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.)

There is no specific information available at present concerning the use of epirubicin hydrochloride in human pregnancy. However, as it has been shown to be embryotoxic and fetotoxic in animals. Women of child-bearing potential should avoid becoming pregnant during treatment and should use effective contraceptive methods. If the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the foetus. ,

Although no studies have been conducted with epirubicin hydrochloride, it may be expected, like doxorubicin, to cause infertility during the period of drug administration. In women, EPIRUBE may cause amenorrhea and premature menopause in premenopausal women. 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 EPIRUBE, the drug could induce chromosomal damage in human spermataozoa; therefore, males undergoing EPIRUBE treatment should employ contraceptive measures.

Men and women should use an effective method of contraception during treatment and for 6 months thereafter.

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.

Effects on ability to drive and use machines

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

INTERACTIONS WITH OTHER MEDICINES

Epirubicin hydrochloride is mainly used in combination with other cytotoxic drugs and additive toxicity may occur especially with regard to bone marrow/ haematological and gastrointestinal effects. In addition, the concomitant use of epirubicin hydrochloride with other antitumour drugs which have been reported as potentially cardiotoxic (e.g. fluorouracil, cyclophosphamide, cisplatin, taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (e.g. calcium channel blockers), required a close monitoring of cardiac function throughout treatment.

If epirubicin hydrochloride is used concomitantly with other drugs that may cause heart failure, eg. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment.

Propranolol: concurrent administration of epirubicin and propranolol may result in an additive cardiotoxic effect.

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.

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

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

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

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

Medicinal products that induce the enzyme cytochrome P-450 (such as rifampicin and barbiturates) can increase the metabolism of epirubicin, resulting in a reduction of the efficacy.

Verapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

The co-administration of interferon α2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre) treatment with medications which influences the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicaol, diphenylhydantoin, amidopyrine-derivative, antiretroviral agents).

Concomitant use with cyclosporin may cause excessive immunosuppression.

ADVERSE EFFECTS

More than 10% of treated patients can expect to develop undesirable effects. The most common undesirable effects are myelosuppression, gastrointestinal side effects, anorexia, alopecia and infection.

More common reactions (>5%):

Haematological
Myelosuppression (leucopenia, granulocytopenia and neutropenia, thrombocytopenia, mild anaemia,

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

Gastrointestinal
Nausea, vomiting, diarrhoea and mucositis (erythema, erosions/ ulcerations, bleeding). Mucositis may appear five to ten 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.

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

Application site
Erythematous streaking along the infused vein.

Infections and infestations
Infection, secondary infection.

Metabolism and Nutrition
Dehydration

Vascular disorders
Hot flashes, phlebitis, thrombophebitis

Less common reactions (<5%):

Haematological
Severe thrombocytopenia, anaemia, severe myelosuppression, pancytopenia, sepsis, septicaemia, septic shock, tissue hypoxia, haemorrhage and death.

Cardiovascular
Cardiomyopathy, CHF (dyspnoea, oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm), cardiomegaly, cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy) atrioventricular and bundle branch block, tachyarrhythmias (premature ventricular contractions, ventricular tachycardia, bradycardia), asymptomatic drops in left ventricular ejection fraction.

Gastrointestinal
Oesophagitis, mucositis, stomatitis, nausea, vomiting, diarrhea, bleeding, hyperpigmentation of oral mucosa and abdominal pain or burning sensation.

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

Application site
Vesication, phlebitis, thrombophlebitis and venous sclerosis. Local pain, severe cellulitis and skin necrosis following perivenous drug extravasation.

Ocular
Conjunctivitis, keratitis.

Hepatic
Changes in transaminase levels.

General
Chills, shock, fever

Immunological Disorders
Anaphylaxis may occur.

Central nervous system
Weakness, dizziness, confusion, depression, paraesthesia.
Metabolism and Nutrition
Hyperuriceamia, anorexia

Hyperuricaemia may occur as a consequence of the extensive purine catabolism which accompanies drug induced rapid cell kill of highly chemosensitive neoplasms (tumour lysis syndrome). Hydration, urine alkalinisation and allopurinol administration will help to prevent or minimise the adverse effects of hyperuricaemia.

Reproductive Disorders
Amenorrhoea, azoospermia

General disorders and administration site conditions
Malaise/asthenia, fever, chills

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Acute lymphocytic leukemia, acute myelogenous leukemia

Intravesicular administration

As drug absorption is minimal, severe systemic side effects and allergic reactions are rare; more frequently reported are local reactions such as burning sensations and frequent voiding (pollakisuria). Occasional bacteria or chemical cystitis have been reported, sometimes haemorrhagic, and bladder constriction has been observed. These ADR's are mostly reversible. Dose reduction (40%) may be necessary in these cases.

Severe or life-threatening reactions

Myelosuppression

This accompanies effective epirubicin hydrochloride treatment in almost 100% of patients and represents the acute dose limiting toxicity of this drug. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently. Leucopenia is 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. Intravenous antibiotics should be given in the presence of febrile neutropenia.

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 "Dose Modifications").

Other haematological

The occurrence of secondary acute myelogenous leukaemia, with or without a preleukaemic phase, has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines such as epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA damaging antineoplastic agents, or when patients have been heavily pretreated with cytotoxic drugs or when the doses have been escalated. This complication has been reported in 1 to 2% of patients receiving epirubicin containing combination chemotherapy as adjuvant therapy in breast cancer. These leukaemias can have a short (one to three year) latency period.

Mucositis

This is frequent and painful and most commonly develops five to ten days after treatment. It typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and progress to ulceration with a risk of secondary infection. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy. The mucositis usually subsides in ten days.

Cardiotoxicity

The cardiac abnormalities caused by treatment can be separated into two categories: ECG alterations and congestive heart failure (CHF). ECG changes following epirubicin hydrochloride treatment occur in about 10% of patients. The changes are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure.

Epirubicin, like other members of this class of drugs, may cause congestive cardiac failure (cardiomyopathy). This effect is cumulative dose dependent and represents the cumulative dose limiting toxicity of the drug. The following measures may identify patients with early anthracycline cardiomyopathy: progressive flattening or inversion of the T waves (mainly in the left praecordial leads), low QRS voltage, prolonged systolic time interval, reduced ejection fraction (echocardiography or by cardiac gated pool scanning) or cardiac biopsy showing characteristic electromicroscopic changes. Early diagnosis and management may control the heart failure. Epirubicin hydrochloride induced cardiomyopathy can be fatal (see Precautions). Delayed cardiac toxicity is represented by a characteristic cardiomyopathy which clinically is manifested by symptoms/ signs of ventricular dysfunction/ CHF (e.g. dyspnoea, pulmonary oedema, dependent oedema, hepatomegaly, ascites, pleural effusion, gallop rhythm).

Delayed cardiotoxicity mainly develops during the course of therapy with epirubicin and up to two to three months afterwards, but late events (several months to years after treatment termination) have occurred. Pericardial effusion has also been described.

DOSAGE AND ADMINISTRATION

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

If EPIRUBE is administered as a continuous infusion, this should preferably take place via a central venous catheter.

EPIRUBE is for use in one patient on one occasion only. Discard any residue.

Care in the intravenous 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 (see "PRECAUTIONS").

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

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. Epirubicin hydrochloride 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 doctor 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 three to four 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 three to four 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 to 90 mg/m^2) for heavily pretreated patients, patients with pre-existing bone marrow depression or in the presence of neoplastic bone marrow infiltration. If epirubicin hydrochloride 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 eight 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, four weekly administrations of 50 mg followed by eleven 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 12 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.

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).

Impaired hepatic function
As clinical toxicity may be increased by the presence of impaired liver function, epirubicin hydrochloride dosage must be reduced if hepatic function is impaired, according to Table 1.

Epirubicin Hydrochloride Injection **Table 1**
Dosage in hepatic impairment

Serum bilirubin levels	Recommended dose
20 - 50 micromol/L	½ normal dose
Over 50 micromol/L	¼ normal dose

Haematological toxicity
Dosage reduction, delay or suspension of therapy with epirubicin hydrochloride may be necessary.

Concurrent antineoplastic agents
Lower doses may be necessary if epirubicin hydrochloride is used concurrently with other antineoplastic agents.

Pharmaceutical Precautions of Solution (See Warnings)

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

- Personnel should be trained in good technique for handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling epirubicin hydrochloride 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 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.

Administration

EPIRUBE Injection should be stored at 2 °C to 8 °C (Refrigerate, do not freeze). The product contains no antimicrobial preservative.

The product does not contain a preservative. Use in one patient on one occasion only. Discard any residue.

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

EPIRUBE Injection can be further diluted with sterile water for injections.

Intravenous administration

It is recommended that EPIRUBE 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. However, the dosage should be administrated in not less than three to four minutes to minimise the risk of thrombosis and perivenous extravasation. 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 "PRECAUTIONS").

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 discontinued. The patient's pain may be relieved by cooling down the area and keeping it cool for 24 hours. Local infiltration with corticosteroids, with or without the combination of a sodium bicarbonate solution (8.4%) and local application of dimethyl sulfoxide and cold packs have been used with various degrees of success. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks after extravasation occurs.

Intravesical administration

The solution of EPIRUBE, to be instilled using a catheter, should be retained intravesically for one 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.

Administration of epirubicin may produce symptoms of chemical cystits (such as dysuria, polyuria, nocturia, stranguria, haematuria, 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 tumours).

Compatibility

EPIRUBE is compatible with the following infusion media:

- 0.9 % sodium chloride
- 5% glucose,
- 0.9% sodium chloride with 5% glucose.

EPIRUBE can be used in combination with other antitumour agents, but it is not recommended that it be mixed with these drugs in the same container.

EPIRUBE should not be mixed with heparin as these drugs are incompatible. Until specific compatibility data are available, it is not recommended that epirubicin hydrochloride be mixed with other drugs.

OVERDOSAGE

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section "Special warnings and precautions for use"). Patients must be carefully monitored. If signs of cardiac failure occur patients should be treated according to conventional guidelines.

Treatment is symptomatic. Epirubicin cannot be removed by dialysis.

Case Study
A 36 year old man with non-Hodgkin's lymphoma received daily epirubin injection 95 mg/m^2 for five 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 dose of epirubicin 320 mg/m^2, 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.

Symptoms

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

Treatment

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 from toxicities. Delayed cardiac failure may occur up to six 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.

In case of overdose, immediately contact the Poisons Information Centre for advice (in Australia call 131 126).

PRESENTATION

Solution for injection in vials: 10 mg/5mL, 20 mg/10mL, 50 mg/25mL, 150 mg/75mL and 200 mg/100mL in packs of 1's.

STORAGE

Store at 2°C to 8°C. Refrigerate. Do not freeze. Store in the original container.

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 a mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15-25°C).

SPONSOR

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POISONS SCHEDULE

S4 (Prescription Only Medicine)

Date of TGA approval: 17 November 2009
Date of most recent amendment: 17 August 2016