PRODUCT INFORMATION

PHARMORUBICIN® RD

(Powder for Injection 50 mg)

PHARMORUBICIN® Injection

(10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL and 200 mg/100 mL)

NAME OF THE DRUG

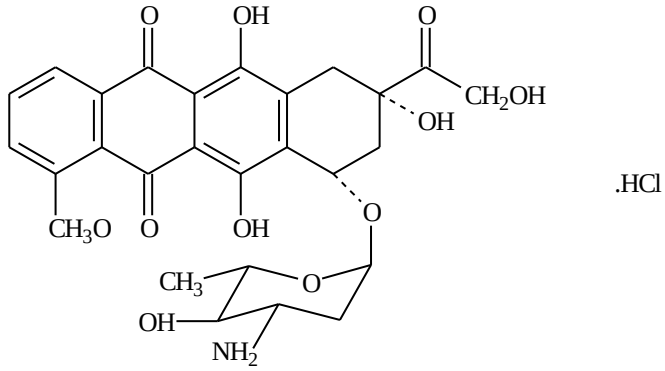
Epirubicin hydrochloride

DESCRIPTION

PHARMORUBICIN (epirubicin hydrochloride) is supplied in two presentations: as a lyophilised powder with a rapid dissolution formulation containing methyl hydroxybenzoate and lactose (PHARMORUBICIN RD Powder for Injection) and as a ready-to-use solution (PHARMORUBICIN Injection).

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.

The structural formula is:



CAS 56390-09-1

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

PHARMACOLOGY

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.

Like most other antitumour and immunosuppressant agents, PHARMORUBICIN, 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 PHARMORUBICIN 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 75–90 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 per cent 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, PHARMORUBICIN may not be expected to cross the blood-brain barrier. When PHARMORUBICIN 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.

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/flurorouracil (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.

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).

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 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 infections
- inflammation of the bladder
- catheterisation problems
- haematuria

PRECAUTIONS

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 (eg ≥90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (eg <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 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 PHARMORUBICIN treatment.

Warnings

BOTH PHARMORUBICIN INJECTION AND POWDER FOR INJECTION MUST BE HANDLED WITH CARE. IF EITHER OF THE PREPARATIONS 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.

HaematologicToxicity

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 DOSAGE AND ADMINISTRATION, Dose Modifications, *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 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 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 INTERACTIONS WITH OTHER MEDICINES). 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 to27 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with epirubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

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

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 DOSAGE AND ADMINISTRATION). Patients with severe hepatic impairment should not receive PHARMORUBICIN (see CONTRAINDICATIONS).

Renal Function

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 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 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.

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.

Excipients

PHARMORUBICIN RD Powder for Injection contains methyl hydroxybenzoate. This may cause allergic reactions (which may occur after treatment), and in rare cases, respiratory difficulties.

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)

Women of child-bearing potential should be advised to avoid becoming pregnant during treatment and should use effective contraceptive methods.

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.

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 spermataozoa; therefore, males undergoing PHARMORUBICIN treatment should employ contraceptive measures.

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.

INTERACTIONS WITH OTHER MEDICINES

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 (eg. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, trastuzumab), as well as the concomitant use of other cardioactive compounds (eg. calcium channel blockers), requires a close monitoring of cardiac function throughout treatment.

Propranolol: 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. Coadministration 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.

ADVERSE EFFECTS

Dose limiting toxicities are myelosuppression and cardiotoxicity (described in detail under PRECAUTIONS).

Adverse effects observed are:

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

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

Administration site conditions: vesication. Local pain, severe cellulitis and skin necrosis following perivenous drug extravasation.

Eye disorders: conjunctivitis, keratitis

General disorders: chills, fever, , malaise/asthenia,

Immune system disorders anaphylaxis

Investigations: asymptomatic drops in left ventricular ejection fraction, changes in transaminase levels

CNS: weakness, dizziness, confusion, depression, paresthesia.

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 Surveillance

Infections and infestations: pneumonia

Renal and urinary disorders: red coloration 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.

DOSAGE AND ADMINISTRATION

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

Care in the intravenous administration of PHARMORUBICIN will reduce the chance of perivenous infiltration (see PRECAUTIONS, *Extravasation*). It may also decrease the chance of local reactions, such as urticaria and erythematous streaking.

NOTE: The recommended lifetime cumulative dose limit of PHARMORUBICIN is 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. 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 pretreated 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.

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: 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.

Preparation of Solution (see Warnings)

PHARMORUBICIN is available in two presentations: a ready-to-use solution 'PHARMORUBICIN Injection' (10 mg, 20 mg 50 mg and 200 mg; at a strength 2 mg/mL) and a lyophilised powder with a rapid dissolution formula containing lactose and methyl hydroxybenzoate, 'PHARMORUBICIN Powder RD for Injection' (50 mg).

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 (15 – 25^{o}C).

PHARMORUBICIN RD Powder for Injection should be dissolved in sterile Water for Injections or Sodium Chloride Injection as indicated in the table below:

Freeze-dried Vial	Diluent Added	Final Concentration
50 mg	25 mL	2 mg/mL

For intravesical administration the desired dose of PHARMORUBICIN RD Powder for Injection should be dissolved in 50 mL of sterile Water for Injections or Sodium Chloride Injection.

Particular care should be taken to avoid aerosol formation when inserting the needle during reconstitution. Inhalation of any aerosol produced during reconstitution must be avoided. After adding the diluent, the vial should be shaken and the contents allowed to dissolve.

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.

PHARMORUBICIN RD Powder for Injection contains methyl hydroxybenzoate. Reconstituted solution should be used immediately or as soon as practicable after reconstitution in order to reduce the microbiological hazard. If storage is necessary, store at 2°C to 8°C for not more than 24 hours. Any unused solution should be discarded.

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

Intravenous Administration

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 PRECAUTIONS, *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.

Compatibility

PHARMORUBICIN is compatible with the following infusion media:

- 0.9% Sodium Chloride
- 5% Glucose
- 0.9% Sodium Chloride with 5% Glucose.

PHARMORUBICIN 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.

Heparin: PHARMORUBICIN should not be mixed with heparin as these drugs are incompatible. Until specific compatibility data are available, it is not recommended that PHARMORUBICIN be mixed with other drugs.

OVERDOSAGE

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 leukopenia and thrombocytopenia) within 10-14 days and also gastrointestinal toxic effects (mainly mucosititis).

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.

Contact the Poisons Information Centre in Australia on 131126 for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

PHARMORUBICIN (epirubicin hydrochloride) for injection is available in two presentations, packaged and supplied as single vial cartons:

PHARMORUBICIN RD Powder for Injection is supplied in vials containing 50 mg of epirubicin hydrochloride as a red lyophilised powder for reconstitution before use.

Excipients: lactose and methyl hydroxybenzoate.

PHARMORUBICIN Injection is supplied in vials containing 10 mg^, 20 mg^, 50 mg and 200 mg of epirubicin hydrochloride (strength 2 mg/mL) as a ready-to-use solution.

Excipients: sodium chloride, water for injections.

^ These presentations are not marketed.

PHARMORUBICIN RD Powder for Injection should be stored below 25°C.

PHARMORUBICIN Injection should be stored at 2°C to 8°C. Refrigerate, do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
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West Ryde NSW 2114
Australia

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

23 September 1991

DATE OF MOST RECENT AMENDMENT

17 June 2014

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