1 NAME OF THE MEDICINAL PRODUCT

Pharmorubicin 2 mg/ml Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Epirubicin hydrochloride 2 mg per ml

5 ml vials contain 10 mg of epirubicin hydrochloride
25 ml vials contain 50 mg of epirubicin hydrochloride
100 ml vials contain 200 mg epirubicin hydrochloride.

Excipient with known effect
Pharmorubicin 10 mg/5 ml (2 mg/ml) solution for injection or infusion contains 17.7 mg of sodium in each 5 ml vial.

Pharmorubicin 50 mg/25 ml (2 mg/ml) solution for injection or infusion contains 88.5 mg of sodium in each 25 ml vial.

Pharmorubicin 200 mg/100 ml (2 mg/ml) solution for injection or infusion contains 354 mg of sodium in each 100 ml vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Red, sterile, preservative-free, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pharmorubicin has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma.

Intravesical administration of Pharmorubicin has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Posology

Pharmorubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

It is advisable to give the drug via the tubing of a freely-running IV saline infusion after checking that the needle is well placed in the vein. This method minimises the risk of drug extravasation and makes sure that the vein is flushed with saline after the administration of the drug. Extravasation of Pharmorubicin from the vein during injection may give rise to severe tissue lesions, even necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Conventional doses:
When Pharmorubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body area; the drug should be injected I.V. over 3-5 minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

High doses:
Pharmorubicin as a single agent for the treatment of lung cancer at high doses should be administered according to the following regimens:

Lung cancer
- Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.

- Non small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day 1 or 45 mg/m^2 days 1, 2, 3, every 3 weeks.

Breast cancer

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m2 (as a single dose on day 1) to 120 mg/m2 (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

The drug should be given as an I.V. bolus over 3-5 minutes or as an infusion up to 30 minutes. Lower doses (60-75 mg/ m^2 for conventional treatment and 105-120 mg/ m^2 for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Pharmorubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4 - 3 mg/100 ml) requires a 50% reduction of dose, while severe impairment (bilirubin > 3mg/100 ml) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Pharmorubicin excreted by this route.

Intravesical administration:
Pharmorubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be used in this way for the treatment of invasive tumours which have penetrated the bladder wall where systemic therapy or surgery is more appropriate. Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg/50 ml. For prophylaxis, 4 x weekly administrations of 50 mg/50 ml, followed by 11 x monthly instillations at the same dosage, is the schedule most commonly used.

The solution should be retained intravesically for 1 hour. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void at the end of the instillation time.

4.3 Contraindications

Hypersensitivity to epirubicin or to any of the excipients listed in section 6.1, other anthracyclines or anthracenediones.

- Lactation

Intravenous use:

- persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency
- recent myocardial infarction
- severe arrhythmias
- previous treatments with maximum cumulative doses of epirubicin and/or other anthracyclines and anthracenediones (see section 4.4)
- patients with acute systemic infections
- unstable angina pectoris
- myocardiopathy

Intravesical use:

- urinary tract infections
- inflammation of the bladder
- haematuria
- invasive tumours penetrating the bladder
- catheterisation problems

4.4 Special warnings and precautions for use

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

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

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

Cardiac Function - Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events.

Early (i.e., Acute) Events. Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin treatment.

Late (i.e., Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as 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.

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 (see section 5.1).

Cardiac function should be assessed before patients undergo treatment with epirubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

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

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section 4.5) with an increased risk in the elderly.

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving trastuzumab therapy alone or in combination with anthracyclines such as epirubicin. This may be moderate to severe and has been associated with death.
Trastuzumab and anthracyclines such as epirubicin should not be used currently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with trastuzumab treatment, although the risk is lower than with concurrent use of traztuzumab and anthracyclines.

The reported half-life of trastuzumab is variable. The substance may persist in circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

If symptomatic cardiac failure develops during trastuzumab therapy after epirubicin therapy, it should be treated with the standard medications for this purpose.

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 foetal/neonatal cardiotoxic events including foetal death following in utero exposure to epirubicin (see section 4.6).

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

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 leucopoenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopoenia and neutropenia are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10 and 14 after drug administration; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include pyrexia, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary Leukaemia - Secondary leukaemia, with or without a preleukaemic 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, in combination with radiation treatment, 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. (See section 5.1).

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

Liver Function **-** The major route of elimination of epirubicin is the hepatobiliary system. Serum total bilirubin and AST levels should be evaluated before and during treatment with epirubicin. Patients with elevated bilirubin or AST may experience slower clearance of drug with an increase in overall toxicity. Lower doses are recommended in these patients (see sections 4.2 and 5.2). Patients with severe hepatic impairment should not receive epirubicin (see section 4.3).

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

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

Extravasation **-** Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately discontinued. The adverse effect of extravasation of anthracyclines may be prevented or reduced by immediate use of a specific treatment e.g. dexrazoxane (please refer to relevant labels for use). The patient's pain may be relieved by cooling down the area and keeping it cool using hyaluronic acid and DMSO. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks extravasation occurs, a plastic surgeon should be consulted with a view to possible excision.

Other **-** As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of epirubicin

Tumour-Lysis Syndrome - Epirubicin may induce hyperuricemia 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 hyperuricemia may minimize 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, (see section 4.5). 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.

Reproductive system - Epirubicin can cause genotoxicity. Men and women treated with epirubicin should adopt appropriate contraceptives during and for a period after treatment with epirubicin (see section 4.6). Patients desiring to have children after completion of therapy should be advised to obtain genetic counselling if appropriate and available.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical route - Administration of epirubicin may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder

discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterization problems (e.g., ureteral obstruction due to massive intravesical tumours).

Intra-arterial route - Intra-arterial administration of epirubicin (transcatheter arterial embolisation for the localized or regional therapies of primary hepatocellular carcinoma or liver metastases) may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of epirubicin) localized or regional events which include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

Excipient with known effect
This medicinal product may be further prepared for administration with sodium containing solutions (see section 4.2 and section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

Excipient information
Pharmorubicin 10 mg/5 ml (2 mg/ml) solution for injection or infusion contains 17.7 mg of sodium in each 5 ml vial, equivalent to 0.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Pharmorubicin 50 mg/25 ml (2 mg/ml) solution for injection or infusion contains 88.5 mg of sodium in each 25 ml vial, equivalent to 4.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Pharmorubicin 200 mg/100 ml (2 mg/ml) solution for injection or infusion contains 354 mg of sodium in each 100 ml vial, equivalent to 17.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is mainly used in combination with other cytotoxic drugs. Additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see section 4.4). The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

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

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 reported half-life of trastuzumab is variable. The substance may persist in circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If this is not possible, the patient's cardiac function should be monitored carefully.

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 epirubicin by 50% and should be discontinued during treatment with epirubicin

When given prior to epirubicin, paclitaxel can cause increased plasma concentrations of unchanged epirubicin and its metabolites, the latter being, however, neither toxic nor active. Co-administration of paclitaxel or docetaxel did not affect the pharmacokinetics of epirubicin when epirubicin was administered prior to the taxane.
This combination may be used if using staggered administration between the two agents. Infusion of epirubicin and paclitaxel should be performed with at least a 24 hour interval between the 2 agents.

Dexverapamil 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, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, antiretroviral agents).

Increase of myelosuppression may occur in patients receiving combination therapy of anthracycline and dexrazoxane.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no studies in pregnant women. Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman, particularly in the first trimester.

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

Epirubicin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is not known whether epirubicin is excreted in human milk. Because many drugs, including other anthracyclines, are excreted in human milk and 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.

Fertility
Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should seek advice on sperm preservation due to the possibility of irreversible infertility caused by therapy.

Epirubicin may cause amenorrhea or premature menopause in premenopausal women.

Based on animal studies, male and female fertility may be compromised (see section 5.3). It is recommended to discuss fertility preservation with men and women prior to treatment.

Women of childbearing potential/ Contraception in males and females
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.

Men undergoing treatment with epirubicin should be advised to use effective contraceptive methods during treatment and for at least 3.5 months after the last dose.

4.7 Effects on ability to drive and use machines

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin with the following frequencies:

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Fre kno (car esti fro ava**
Infections and infestations	Infection, Conjunctivitis		Sepsis,* Pneumonia*			
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Acute myeloid leukaemia, Acute lymphocytic leukaemia			
Blood and lymphatic system	Anaemia, Leukopenia, Neutropenia,					

System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Very Rare < 1/10,000**	**Fre kno (car esti fro ava**
disorders	Thrombocytopenia Febrile neutropenia					
Immune system disorders				Anaphylactic reaction*		
Metabolism and nutrition disorders		Decreased appetite Dehydration*		Hyperuricaemia*		
Eye disorders	Keratitis					
Cardiac disorders		Ventricular tachycardia, Atrioventricular block, Bundle branch block, Bradycardia, Cardiac failure congestive				
Vascular disorders	Hot flush, Phlebitis*	Haemorrhage,* Flushing*	Embolism, Embolism arterial,* Thrombophlebitis*			Sho
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			
Gastrointestinal disorders	Nausea, Vomiting, Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain,* Gastrointestinal erosion,* Gastrointestinal ulcer*	Gastrointestinal haemorrhage*			Abd disc Pigr buc
Skin and subcutaneous tissue disorders	Alopecia, Skin toxicity	Rash/Pruritus, Nail pigmentation,* Skin disorder, Skin hyperpigmentation*	Urticaria* Erythema*			Pho reac
Renal and urinary disorders	Chromaturia*†					
Reproductive system and breast disorders	Amenorrhoea					
General disorders and administration site conditions	Malaise, Pyrexia*	Chills*	Asthenia			
Investigations	Transaminases abnormal	Ejection fraction decreased				

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Fre kno (car esti fro ava
Injury, poisoning and procedural complications	Chemical cystitis*§					Rec phe

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leucopoenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucosal inflammation) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment:
Symptomatic. Epirubicin cannot be removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances, ATC code: L01DB03

The mechanism of action of Pharmorubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Pharmorubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after I.V. injection of 60-150mg/m^2 of the drug follow a tri-exponential decreasing

pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. The major metabolites that have been identified are epirubicinol (13-OH-epirubicin) and glucuronides of epirubicin and epirubicinol.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH-derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged drug.

Pharmorubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.

Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The drug does not cross the blood-brain barrier.

5.3 Preclinical safety data

The main target organs of toxicity following administration of epirubicin to animals were the haemolymphopoietic system, GI tract, heart, kidney, liver and reproductive organs.

It was genotoxic, and, like other anthracyclines, carcinogenic in rats.

Epirubicin was toxic to male and female reproductive organs in animal studies. In male rats, administration of epirubicin caused decreases in size/weight of the testes and/or epidiymides, and reduced spermatogenesis. In females, epirubicin caused gross alterations in the ovaries and uteri in rats and uterine atrophy in rats and dogs.

Epirubicin was embryotoxic and teratogenic when administered during the period of organogenesis in pregnant rats, with an increased incidence of visceral abnormalities observed. No malformations were observed in rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.

A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid

Sodium chloride

Water for Injections

6.2 Incompatibilities

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

Pharmorubicin should not be mixed with heparin due to chemical incompatibility which may lead to precipitation when the drugs are in certain proportions.

Pharmorubicin can be used in combination with other antitumour agents, but it is not recommended that it be mixed with other drugs.

6.3. Shelf-life

a) Shelf life of the product as package for sale:

Glass vials: 3 years

b) Shelf life after first opening the container:

Pharmorubicin Solution for Injection does not contain a preservative or bacteriostatic agent. Vials are, therefore for single use only and any unused portion must be discarded after use.

From a microbiological point of view, the product should be used immediately after first penetration of the rubber stopper. If not used immediately, in use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store at 2°C - 8°C (in a refrigerator)
Keep the vial in the outer carton in order to protect from light.

Storage of the solution for injection or infusion 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 2 to a maximum of 4 hours equilibration at controlled room temperature (15 - 25°C). Solution for injection or infusion should be used within 24 hours after removal from refrigeration.

6.5 Nature and contents of container

Type I clear glass 10ml, 25ml, or 100ml vial (type I), with siliconised halobutyl rubber stoppers and aluminium cap with opaque, coloured plastic flip-off top.

6.6 Special precautions for disposal

***Intravenous administration*.** Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride). To minimize the risk of thrombosis or perivenous extravasation, the usual infusion times range between 3 and 20 minutes depending upon dosage and volume of the infusion solution. A direct push injection is not recommended

due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration (see section 4.4).
Discard any unused solution.

***Intravesical administration*.** Epirubicin should be instilled using a catheter and retained intravesically for 1 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

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

Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling epirubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system); the work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. In case of contact with the eye(s), hold back the eyelid of the affected eye(s) and flush with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 May 2004

10 DATE OF REVISION OF THE TEXT

14/04/2021