SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin hydrochloride 2 mg/ml intravesical solution/solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 2 mg of Epirubicin hydrochloride.

1 vial with 5 ml solution for injection of Epirubicin contains 10 mg epirubicin hydrochloride.
1 vial with 10 ml solution for injection of Epirubicin contains 20 mg epirubicin hydrochloride.
1 vial with 25 ml solution for injection of Epirubicin contains 50 mg epirubicin hydrochloride.
1 vial with 100 ml solution for injection of Epirubicin contains 200 mg epirubicin hydrochloride.

Excipients with known effect:
Epirubicin 10 mg/5 ml
This medicine contains less than 1 mmol sodium (23 mg) in each vial.

Epirubicin 20 mg/10 ml
This medicine contains 34.48 mg sodium in each vial.

Epirubicin 50 mg/25 ml
This medicine contains 86.19 mg sodium in each vial.

Epirubicin 200 mg/100 ml
This medicine contains 344.73 mg sodium in each vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intravesical solution/Solution for injection

A clear red solution.

pH: 2.5 – 3.5

Osmolality: 270 – 330mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin is used in the treatment of a range of neoplastic conditions including;

- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of;

- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.

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

Intravenous administration (IV)

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 Epirubicin 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 dose

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

High dose

Epirubicin hydrochloride 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/m2 day 1, every 3 weeks.

Breast cancer

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin hydrochloride ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (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 treatment) are recommended for patients whose bone marrow function has 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 Epirubicin hydrochloride 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 epirubicin excreted by this route.

Intravesical administration

Epirubicin 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 intravesical 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 urine at the end of the instillation time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or 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 hydrochloride (e.g., $\geq$ 90 mg/m^2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m^2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin hydrochloride does require special attention for possible clinical complications due to profound myelosuppression.

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

Early (i.e. Acute) Events. Early cardiotoxicity of epirubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia, and bradycardia, as well as

atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for the discontinuation of epirubicin treatment.

Late (i.e. Delayed) Events. Delayed cardiotoxicity usually develops late in the course of therapy with epirubicin or within 2 to 3 months after treatment termination, but later events (several months to years after completion of treatment) have also been reported. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as 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 hydrochloride in excess of 900 mg/m^2; this cumulative dose should only be exceeded with extreme caution (see section 5.1).

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

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

Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, 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 trastuzamab 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 trastuzumab and anthracyclines.

Because the half-life of trastuzumab is approximately 28-38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping trastuzumab treatment. Patients who receive anthracyclines such as epirubicin after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping trastuzumab. If anthracyclines such as epirubicin are used, the patient's cardiac function should be monitored carefully (see section 4.5).

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**.**

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

Hematologic Toxicity - As with other cytotoxic agents, epirubicin may produce myelosuppression. Hematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopoenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic 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 fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary Leukaemia – *S*econdary leukaemia, with or without a preleukemic 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 leukaemia's can have a 1- to 3-year latency period. (See section 5.1).

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

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

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

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

Extravasation **-** Extravasation of epirubicin during intravenous injection may produce local pain, severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of epirubicin, the drug infusion should be immediately 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, use of 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. 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., uretheral obstruction due to massive intravesical tumors).

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.

Important information about some of the ingredients of Epirubicin Hikma

Epirubicin 10 mg/5 ml

This medicine contains less than 1 mmol sodium (23 mg) in each vial, that is to say essentially ‘sodium-free’.

Epirubicin 20 mg/10 ml

This medicine contains 34.48 mg sodium per vial, equivalent to 1.72% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Epirubicin 50 mg/25 ml

This medicine contains 86.19 mg sodium per vial, equivalent to 4.31% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Epirubicin 200 mg/100 ml

This medicine contains 344.73 mg sodium per vial, equivalent to 17.24% 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/hematologic and gastro-intestinal effects (see section 4.4). The use of epirubicin in combination chemotherapy with other potentially cardiotoxic drugs, as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires monitoring of cardiac function throughout treatment.

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

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.

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. Coadministration 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

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

Experimental data in animals suggest that epirubicin may cause foetal harm when administered to a pregnant woman. If epirubicin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus.

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

Breastfeeding

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, mothers should discontinue nursing prior to taking this drug.

Fertility

Epirubicin could induce chromosomal damage in human spermatozoa. Men undergoing treatment with epirubicin should use effective contraceptive methods and if appropriate and available, 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.

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**	**Frequency not known (cannot be estimated from the available data)**
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 disorders	Anaemia, Leucopoenia, Neutropenia, 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*			Shock*
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			
Gastrointestinal disorders	Nausea, Vomiting, Stomatitis, Mucosal inflammation, Diarrhoea	Gastrointestinal pain,* Gastrointestinal erosion,* Gastrointestinal ulcer*	Gastrointestinal haemorrhage*			Abdominal discomfort, Pigmentation buccal*
Skin and subcutaneous tissue disorders	Alopecia, Skin toxicity	Rash/Pruritus, Nail pigmentation,* Skin disorder, Skin hyperpigmentation*	Urticaria* Erythema*			Photosensitivity reaction*
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				
Injury, poisoning and procedural complications	Chemical cystitis*§					Recall phenomenon*Δ

* ADR identified post-marketing.
† Red coloration of urine for 1 to 2 days after administration.
§ Following intravesical administration.

[Δ] Hypersensitivity to irradiated skin (radiation-recall reaction).

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, Website: 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 leukopenia 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

Pharmacoterapeutic group: Group 16.1.6 – Antineoplastic agent.

Cytotoxics. Intercalating DNA cytotoxics, ATC code: L01D B03

The mechanism of action of epirubicin 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. Epirubicin 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 intravenous injection of 60-150 mg/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.

Epirubicin 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 in rat, rabbit and dog following repeated dosing were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the species tested.
It was genotoxic, and, like other anthracyclines, carcinogenic in rats. Epirubicin was embryotoxic in rats. No malformations were seen in rats or 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

Sodium lactate (50% solution)

Hydrochloric acid (1N) for pH adjustment

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, which includes sodium bicarbonate containing solutions. Only the diluents detailed in section 6.3 should be used.

Neither Epirubicin injection nor any Epirubicin diluted solutions should be mixed with any other drugs. Epirubicin should not be mixed with heparin due to physical incompatibility (precipitation).

6.3 Shelf life

3 years

Chemical and physical stability was demonstrated, after dilution in Sodium Chloride 0.9% or Glucose 5% solution, for 72 hours when stored in a refrigerator.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store and transport refrigerated (2ºC-8ºC)

Store in the original container protected from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear vials (glass Type I) with chlorobutyl rubber stoppers and aluminium cap.

<u>10 mg/5 ml</u>

Packs with 1 vial containing 5 ml solution

<u>20 mg/10 ml</u>

Packs with 1 vial containing 10 ml solution

<u>50 mg/25 ml</u>

Packs with 1 vial containing 25 ml solution

200 mg/100 ml

Packs with 1 vial containing 100 ml solution

Not all packs may be marketed.

6.6 Special precautions for disposal

Epirubicin may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Intravenous administration
Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or glucose 5%). 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.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.

2. Preparation of an infusion solution should be performed in a designated aseptic area.

3. Adequate protective disposable gloves, goggles, gown and mask should be worn.

4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.

5. 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. Always wash hands after removing gloves.

6. 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 detailed below.

7. Pregnant staff should not handle the cytotoxic preparation.

8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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