SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial of 5 ml of solution contains 10 mg of epirubicin hydrochloride.
Each vial of 10 ml of solution contains 20 mg of epirubicin hydrochloride.
Each vial of 25 ml of solution contains 50 mg of epirubicin hydrochloride.
Each vial of 50 ml of solution contains 100 mg of epirubicin hydrochloride.
Each vial of 100 ml of solution contains 200 mg of epirubicin hydrochloride.

Excipient(s) with known effect
Epirubicin 2 mg/ml, solution for injection contains sodium (3.6 mg/ml or 0.16 mmol/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin Hydrochloride 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 Epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

This medicinal product is intended solely for intravenous or intravesical use.

The safety and efficacy of epirubicin in children and adolescents has not been investigated.

Intravenous administration

Posology

To avoid cardiotoxicity, a total cumulative dose of 900-1000 mg/m^2 of epirubicin hydrochloride should not be exceeded (see section 4.4).

The amount of the total dose in one cycle depends on the mode of use (i.e., as a single therapy or as a combination with other cytotoxic substances) and on the indication.

Standard Posology
In monotherapy, the recommended dosage adults is 60-90 mg/m² of body surface area. Epirubicin Hydrochloride should be injected intravenously. over 3-5 minutes. The dosage should be repeated every 21 days, depending on the patient's blood count and bone marrow function.

If signs of toxicity occur, including severe neutropenia/neutropenic fever and thrombocytopenia (which may persist until day 21), a dose adjustment or postponement of the next subsequent dose may be required.

High Posology

Small cell lung cancer (not previously treated)
When used as monotherapeutic agent for high-dose treatment of lung cancer, epirubicin hydrochloride should be used in accordance with the following schedule: 120 mg/m^2 of body surface area on day 1; every 3rd week.

With high-dose treatment, epirubicin hydrochloride may be administered as an intravenous bolus injection over 3–5 minutes or as an infusion for up to 30 minutes.

Breast Cancer

- Treatment of advanced breast cancer
  Up to 135 mg/m^2 of body surface area of epirubicin hydrochloride in monotherapy and up to 120 mg/m^2 of body surface area in combination therapy on day 1, every 3–4 weeks.
- For adjuvant treatment of patients at early stages of the disease with positive lymph node findings, intravenous epirubicin hydrochloride doses of 100 mg/m^2 of body surface area (as a single dose on day 1) and 120 mg/m^2 (divided into two doses on day 1 and day 8) are recommended

every 3–4 weeks in combination with the intravenous administration of cyclophosphamide and 5-fluorouracil, as well as oral administration of tamoxifen.

Lower doses (60-75 mg/m² with standard dosages and 105-120 mg/m² for high dosages) are recommended in patients whose bone marrow function has been compromised through previous chemotherapy or radiotherapy, through age, or through neoplastic infiltration of the bone marrow. The total dose for one cycle may be administered on 2-3 consecutive days.

The following doses of epirubicin hydrochloride are commonly used in monotherapy and combination chemotherapy for the treatment of various other types of tumour:

Cancer Indication	**Epirubicin Hydrochloride Dosage (mg/m^2)[a]**	
	Monotherapy	**Combination Therapy**
Advanced ovarian cancer	60-90	50-100
Gastric cancer	60–90	50
Small cell lung cancer	120	120
Bladder cancer	Intravesical administration of 50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prevention: 50 mg/50 ml once per week over 4 weeks then once per month over 11 months	

[a] The doses are normally administered on day 1 or day 1, 2 and 3 in 21-day intervals

Combination therapy

When the drug is used in combination with other cytotoxic medicinal products, the dosage must be adjusted accordingly. The dosages commonly used are provided in the table above.

Specific Dosage Instruction

Renal impairment

Although no specific dosage recommendations can be made for patients with impaired renal function due to a lack of data, initial dosages should be reduced in patients with severe renal impairment (serum creatinine >5 mg/dl).

Hepatic impairment

In patients with impaired liver function (bilirubin 1.2–3 mg/100 ml or BSP retention 9–15%), a reduction of the initial dose by 50% is advisable. With

severely impaired liver function (bilirubin >3 mg/100 ml or BSP retention >15%), a reduction in the initial dose by 75% is required.
Patients with severe hepatic impairment must not be administered epirubicin hydrochloride (see section 4.3).

Paediatric population
The safety and efficacy of this medicinal product in children has not been established.

Other patient groups

In patients with severe previous treatment or patients with neoplastic bone marrow infiltration, a dose reduction or an extension of the intervals between the cycles may be necessary (see section 4.4).

Intravesical administration
Epirubicin hydrochloride can be administered intravesically for the treatment of superficial bladder cancer and carcinoma-in-situ, and as a prophylaxis to prevent recurrence following transurethral resection. It must not be administered intravesically to treat invasive tumours that have penetrated the urinary bladder wall (see section 4.3); systemic or surgical treatment is more appropriate in these situations.

Different dosing schedules are used. The following can be used as guidelines:

Superficial bladder cancer: bladder irrigation weekly with 50 mg/50 ml (diluted with a physiological saline solution or with sterile water) for 8 weeks. A reduction in the dose of 30 mg per 50 ml is recommended in the event of local toxicity (chemical cystitis).

Carcinoma in situ: up to 80 mg/50 ml (depending on the tolerance for the patient)

A recurrence prophylaxis following transurethral resection: Administration of 50 mg/50 ml 4 times weekly followed by instillation of the same dose 11 times monthly

The patient should not ingest any more liquid 12 hours before instillation in order to prevent any unwanted dilution with the urine. This should limit urine production to around 50 ml per hour. The patient must be rotated one quarter of a turn every 15 minutes in situ during the drug dwelling time in order to ensure that as much of the bladder mucosa in the pelvis as possible comes into contact with the solution. In general, a period of exposure of one hour is indicated, after which the patient should be encouraged to urinate.

Method of administration

For intravenous or intravesical administration

See also section 6.6 for instructions on dilution of the medicinal product prior to administration.

Epirubicin hydrochloride is generally administered intravenously. Intravesical administration has proven to be well suited for the treatment of superficial bladder cancer as well as in the prophylaxis of tumour recurrence following transurethral resection.

Intravenous administration

Farmorubicin ampoules are not infusion bottles, the contents must be removed with a sterile needle and a syringe. The drug solution is administered as a bolus injection within the scope of a short-term infusion in physiological saline solution. The correct positioning of the infusion needle is checked first of all by administering approx. 5 ml of infusion fluid. The epirubicin solution is then injected into the tube of the infusion applied once the tube has been clamped above the inflow point. This procedure prevents any potential backflow of the epirubicin solution. The total amount of the drug solution is administered slowly via the IV route. Following the application, the tube clamp is removed and rinsing takes place with the rest of the solution for infusion. This technique reduces the risk of thrombosis.

Epirubicin hydrochloride should be introduced into the tube of a free-flowing IV infusion (0.9% sodium chloride or 5% glucose solution). In order to minimise the risk of thrombosis or perivenous extravasation, the duration of the infusion should be between 3 and 20 minutes depending on the dose and volume. A direct puncture is not recommended due to the risk of extravasation, which can occur even with adequate blood return during aspiration.

Intravesical administration
Solutions of 30–80 mg of epirubicin hydrochloride per 50 ml of saline solution are used for intravesical use.

4.3 Contraindications

- Hypersensitivity to the active substance, other anthracyclines or anthracenediones or to any of the excipients listed in section 6.1.
- Breastfeeding periods (see section 4.6).

Intravenous application:
- acute systemic infections
- persistent bone marrow depression
- severe hepatic impairment
- unstable angina pectoris
- severe cardiac failure
- severe arrhythmias
- recently survived myocardial infarction

- myocardiopathy
- previous treatments with epirubicin hydrochloride and/or other anthracyclines and anthracenediones up to the respective maximum cumulative doses (see section 4.4)

Intravesical application:
- urinary tract infections
- inflammation of the bladder
- haematuria
- invasive tumours with penetration of the bladder
- catheterisation problems

4.4 Special warnings and precautions for use

General
Treatment should only be provided under the supervision of doctors with corresponding experience in the treatment of tumours. The medicinal product must be used strictly in accordance with the instructions.

Patients should recover from acute toxic effects of previous cytotoxic therapies (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections) before treatment with epirubicin is initiated.

The adverse events observed during treatment with high doses of epirubicin hydrochloride (e.g., $\geq$ 90 mg/m^2 every 3 to 4 weeks) are comparable with those observed during treatment with standard doses (< 90 mg/m^2 every 3 to 4 weeks). However, the severity of the neutropenia or stomatitis/mucositis may be more pronounced. Treatment with high doses of epirubicin hydrochloride requires particular attention to be paid to possible clinical complications caused by severe bone marrow depression.

Cardiac Function
Cardiotoxicity is a risk linked to treatment with anthracyclines, and may be manifested by early (i.e., acute) or late onset (i.e., delayed) adverse reactions.

Early onset (i.e., acute) adverse reactions (immediate type):
The IMMEDIATE TYPE is independent of dose and characterised by non-specific ECG changes (ST segment depression, sinus tachycardia and supraventricular and ventricular extrasystoles, ventricular tachycardia, and bradycardia, as well as AV block and bundle branch block. These disorders are rarely of clinical relevance, and are generally reversible. The therapy can generally be continued.

Late onset (i.e., delayed) adverse reactions (delayed type):
The DELAYED TYPE is dependent on dose and represents a cumulative organ toxicity in the form of a cardiomyopathy. Delayed cardiotoxicity usually occurs at a later stage or within 2 to 3 months following treatment with epirubicin, although adverse reactions have also been reported that occur at an

even later stage (several months to years after treatment has been completed). Late onset cardiomyopathy is expressed by a reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening congestive heart failure is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The risk of congestive heart failure increases rapidly with an increase in the total cumulative dose of epirubicin hydrochloride that is greater than 900 mg/m^2. This cumulative dose should only be exceeded with extreme caution (see section 5.1).

The cardiac function should be checked before initiating treatment with epirubicin hydrochloride and must also be monitored during the therapy in order to minimize the risk of severe cardiac impairment. This risk can be reduced through regular checks on the left ventricular ejection fraction (LVEF) during the treatment. Epirubicin should be discontinued immediately following the first signs of dysfunction. Quantitative methods for repeated checks on cardiac function (determination of the LVEF) include multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). Checks on cardiac function with an ECG and either a MUGA or echocardiography are recommended before initiating treatment, particularly in patients with risk factors for increased cardiotoxicity. Repeated checks should be performed on the left ventricular ejection fraction by MUGA or echocardiography, particularly at higher, cumulative anthracycline doses. The investigation method used should be the same for all follow-up controls and within the scope of subsequent monitoring.

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

Cardiomyopathy induced by anthracyclines is associated with persistent QRS low voltage, an extension in the systolic time interval above the normal values (PEP) and a decrease in ejection fraction (LVET). Changes in the electrocardiogram (ECG) may indicate anthracycline-induced cardiomyopathy, but the ECG is not a sensitive or a specific method in tracking anthracycline-induced cardiotoxicity.

Risk factors for cardiac toxicity include active or latent cardiovascular disease, previous or concurrent radiotherapy to the mediastinal/pericardial area, previous treatment with other anthracyclines or anthracenediones, concurrent use of other drugs that reduce cardiac contractility or result in cardiotoxicity (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 as a monotherapy or in

combination with anthracyclines such as epirubicin. The heart failure can be moderate to severe and can result in death.

Trastuzumab and anthracyclines such as epirubicin may currently only be given in combination within the scope of a strictly controlled clinical trial setting with cardiological monitoring. In the case of patients who have previously received anthracyclines, there is also a risk of cardiotoxicity following treatment with trastuzumab, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

The reported half-life of trastuzumab is variable. The substance can remain in the bloodstream for up to 7 months. Doctors should therefore 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 heart failure develops during trastuzumab therapy after epirubicin therapy, it should be treated with the appropriate medications for this purpose.

Cardiac function must be monitored particularly closely in patients receiving high cumulative doses and in those patients with risk factors. However, cardiac toxicity from epirubicin can occur even at lower cumulative doses, irrespective of whether there are risk factors present.
There have been isolated reports of cardiotoxic events, including fatal outcomes, in foetuses/newborns after in utero exposure to epirubicin (see section 4.6).
It is probable that the toxicity of epirubicin and other anthracyclines or anthracenediones is additive.

Haematotoxicity
As with other cytotoxic substances, epirubicin can cause bone marrow suppression. The haematological values should be examined before and during each treatment cycle with epirubicin, including differential white blood cell count. Dose-dependent, reversible leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of haemotixicity of epirubicin and is the most common acute dose-limiting toxicity of this substance. Leukopenia and neutropenia are generally more severe with high dosage schedules, with the nadir reached in most cases between the 10^{th} day and 14^{th} day following administration of the substance; they are usually temporary and the leukocyte/neutrophil counts return to normal by the 21^{st} day in most cases. Thrombocytopenia and anaemia may also occur. The clinical consequences of severe bone marrow depression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia, or death.

Secondary Leukaemia
*S*econdary leukaemia, with or without a pre-leukaemic phase, has been observed in patients treated with anthracyclines, including epirubicin. Secondary leukaemia occurs more frequently when these types of substances

are used in combination with DNA-damaging antineoplastic agents or in combination with radiotherapy, if patients have received intensive pre-treatment with cytotoxic substances or if the dosage of the anthracyclines has been increased. These leukaemias can have a 1- to 3-year latency period. (See section 5.1).

Gastrointestinal
Epirubicin is emetogenic. Mucositis and stomatitis generally occur in the early stages following administration and can lead to mucosal inflammation within a few days in severe cases. Most patients recover from this adverse event by the third week of treatment.

Liver Function
Epirubicin is primarily subject to hepatobiliary excretion. Serum levels of total bilirubin and AST should therefore be checked before initiating and during treatment with epirubicin. Clearance may reduce in patients with elevated bilirubin or AST, which may increase toxicity as a whole. Lower doses are recommended therefore with these types of patients (see sections 4.2 and 5.2). The use of epirubicin is contraindicated in patients with severe hepatic impairment (see section 4.3).

Renal Function
Serum creatinine levels should be checked before and during the treatment. A dose adjustment is required in patients with serum creatinine levels > 5 mg/dl (see section 4.2).

Adverse Reactions at Site of Injection
Phlebosclerosis may occur through injection into a small vein or through repeated injections into the same site. Precise adherence to the recommended methods of administration reduces the risk of phlebitis/thrombophlebitis at the injection site (see section 4.2).

Extravasation
Epirubicin hydrochloride should only be administered by safe intravascular injection, as paravenous injection results in local nephrosis and thrombophlebitis.
Extravasation of epirubicin hydrochloride during intravenous injection may cause local pain, severe tissue damage (blisters, severe cellulitis) and necrosis. The infusion should be discontinued immediately if signs and symptoms of extravasation occur during intravenous injection of epirubicin hydrochloride. The adverse reaction of an extravasation of anthracyclines can be prevented or reduced by the immediate introduction of targeted treatment e.g. with dexrazoxane (see the respective summary of product characteristics for instructions for use). The patient’s pain can be alleviated by cooling the affected area with hyaluronic acid and DMSO. The patient should subsequently be monitored very closely as necrosis may occur, including just a

few weeks after extravasation; a plastic surgeon should be consulted regarding any possible excision.

Tumour Lysis Syndrome
Treatment with epirubicin may cause hyperuricaemia due to the high degree of purine catabolism that normally accompanies the rapiddissolution of neoplastic cells (tumour-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated following the initial treatment. Hydration, urinary alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia can minimize the risk of potential complications of tumour-lysis syndrome.

Immunosuppressive Effects/Increased Susceptibility to Infections
Administration of live or live-attenuated vaccines to patients who are immunocompromised from chemotherapy, including epirubicin, can result in serious or potentially lethal infections (see section 4.5). Vaccination with a live vaccine should be avoided during treatment with epirubicin. Dead or inactivated vaccines may be used; however, the immune response to these vaccines may be reduced.

Reproductive system
Epirubicin can cause genotoxicity. Men and women treated with epirubicin must therefore use a reliable contraceptive method during and for a certain length of time 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.

Men who are treated with epirubicin are advised not to father a child during and for a certain length of time after treatment and to seek advice regarding sperm conservation before starting the treatment because of the possibility of irreversible infertility through the therapy. (see section 4.6)

Miscellaneous
As with other cytotoxic preparations, thrombophlebitis and thromboembolic manifestations, including pulmonary embolism (sometimes with a fatal outcome) have been reported following the administration of epirubicin hydrochloride.

<u>Additional warnings and precautions for other types of administration</u>

Intravesical route
The administration of epirubicin hydrochloride may cause symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, strangury, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention must be paid to catheterisation problems (e.g., urethral obstruction due to vesical tumours).

Intra-arterial –

Intra-arterial administration of epirubicin hydrochloride(transcatheter embolisation for local or regional treatments of primary hepatocellular carcinoma or liver metastases) may also cause local or regional events (in addition to systemic toxicity with similar qualitative effects as after the intravenous administration of epirubicin hydrochloride), which may also include gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and stricture of the bile duct due to drug induced sclerosing cholangitis. This route of application can result in extensive necrosis of the perfused tissue.

Excipients

Epirubicin contains sodium.

A 5 ml vial contains 18 mg of sodium, equivalent to 0.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
A 10 ml vial contains 36 mg of sodium, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
A 25 ml vial contains 90 mg of sodium, equivalent to 4.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
A 50 ml vial contains 180 mg of sodium, equivalent to 9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
A 100 ml vial contains 360 mg of sodium, equivalent to 18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product can also be prepared for re-use using sodium-containing solutions (see section 4.2 and 6.6), and this should also be factored into the total sodium from all sources the patient is receiving.

4.5 Interaction with other medicinal products and other forms of interaction

Epirubicin is primarily used in combination with other cytostatic drugs. Additive toxicity may occur particularly with respect to bone marrow/hematological and gastro-intestinal effects (see section 4.4).The use of epirubicin in combination with other potentially cardiotoxic and with other cardioactive substances (e.g., calcium channel blockers), requires continuous monitoring of cardiac functions.

Epirubicin is largely metabolised in the liver. Any concomitant therapy that affects liver function may also influence the metabolism, pharmacokinetics and therapeutic efficacy and/or toxicity of epirubicin (see section 4.4).

Anthracyclines including epirubicin should only be used in combination with cardiotoxic substances if the patient’s cardiac function is being very closely monitored. Patients who receive anthracyclines following discontinuation of treatment with other cardiotoxic agents, particularly those with a long half-life such as trastuzumab, may also be at an increased risk of cardiotoxicity (see section 4.4).

Vaccination with a live vaccine should be avoided in patients receiving epirubicin. Dead or inactivated vaccines may be used; although the immune response to these vaccines may be reduced.

The concomitant administration of cimetidine increases the AUC of epirubicin by 50% and should be discontinued for the duration of the epirubicin treatment.

If paclitaxel is administered before epirubicin, it may increase serum concentrations of epirubicin and its metabolites, whereby the latter are neither toxic nor active. The co-administration of paclitaxel or docetaxel has no effect on the pharmacokinetics of epirubicin provided that epirubicin is administered prior to the taxanes.
Any such combination may be used if the time for administration of both agents is staggered. There should be at least 24 hours between the epirubicin and the paclitaxel infusion.

Dexverapamil may modify the pharmacokinetics of epirubicin and possibly increase its bone marrow suppressive effects.

One study has shown that docetaxel can increase the plasma concentrations of the metabolites of epirubicin if it is administered immediately after epirubicin.

Quinine may accelerate the initial distribution of epirubicin from the blood to the tissues and influence the absorption of epirubicin into the erythrocytes.

Concomitant use with interferon-alpha-2b may result in a reduction in the terminal elimination half-life and the total clearance of epirubicin.

The possibility of a significant disruption of haematopoiesis must be considered in the case of (pre-) treatment with drugs that influence the bone marrow function (i.e. cytostatics, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine derivates, antiretroviral agents).

Bone marrow depression may occur more frequently in patients who are receiving an anthracycline in combination with dexrazoxane.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date, there are only limited experiences on the use of epirubicin in pregnant women. Animal studies have demonstrated reproductive toxicity (see section 5.3).
Epirubicin must not be used during pregnancy, unless the clinical condition of the woman necessitates treatment with epirubicin.

Use during the first trimester of pregnancy should be avoided. Current data on use in humans does not provide any information on the presence or absence of

severe birth defects and miscarriages in connection with the use of epirubicin in the second and third trimester of pregnancy. If epirubicin is administered during pregnancy or if a patient becomes pregnant during treatment, then she should be examined for possible risks to the fœtus.
There are isolated reports of transient ventricular hypokinesia in foetuses and newborns, transient elevated cardiac enzyme levels and cases of foetal deaths due to presumed anthracycline-induced cardiotoxicity after in utero exposure to epirubicin in the second and/or third trimester (see section 4.4).
Corresponding monitoring of the foetus and/or the newborn for signs of cardiotoxicity as well as corresponding checks according to the applicable local standards of care are recommended. Epirubicin should only then be used in pregnancy if the possible benefits of the treatment to the mother justify the possible risks to the foetus.

Breast-feeding
It is not known whether epirubicin passes into breast milk. However, as many medical products, including other anthracyclines, can pass into the breast milk and cause serious adverse reactions among infants, breast-feeding women should be advised not to breast-feed during treatment with epirubicin and for at least 7 days after the last dose.

Fertility

Epirubicin may induce chromosomal damage to human spermatozoa.
Epirubicin may trigger amenorrhoea or early menopause in pre-menopausal women.

Based on animal studies, male and female fertility may be irreversibly impaired (see section 5.3). It is highly recommended to advise men and women prior to initiating treatment on maintaining their fertility.

Women of childbearing potential/contraception for men and women

Women of childbearing potential should be instructed to avoid becoming pregnant during treatment and to use a reliable contraceptive method during treatment and for at least 6.5 months after the last dose.
Men treated with epirubicin should be instructed to use a reliable contraceptive method during treatment and for at least 3.5 months after the last dose.

4.7 Effects on ability to drive and use machines

No studies have been carried out on the effects on the ability to drive or to operate machinery.

4.8 Undesirable effects

The following adverse reactions have been observed and described 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)**	**Not known (Frequency cannot be estimated based on available data)**
Infections and infestations	Infection conjunctivitis		Sepsis* Pneumonia*			Septic shock
Benign, malignant and non-specific neoplasms			Acute myeloid leukaemia Acute lymphocytic leukaemia			
Blood and lymphatic system disorders	Anaemia Leukopenia Granulocytopenia Neutropenia Thrombocytopenia febrile Neutropenia					Haemorrhage and tissue hypoxia as a result of bone marrow depression
Immune system disorders				Anaphylactic reaction*		
Metabolism and nutrition disorders		Reduced appetite Dehydration*		Hyperuricaemia*		
Nervous system disorders				Dizziness		
Eye disorders	Keratitis					
Cardiac disorders		Ventricular tachycardia AV-block bundle Branch block Bradycardia Congestive heart failure		Cardiotoxicity (ECG Anomalies, Arrhythmia, Cardiomyopathy)		

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)	Not known (Frequency cannot be estimated based on available data)
Vascular disorders	Hot flush Phlebitis*	Haemorrhage* Flushing*	Embolism arterial Embolism* Thrombophlebitis*			Shock*
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism*			
Gastrointestinal disorders	Nausea Vomiting Stomatitis Mucosal inflammation Diarrhoea	Gastrointestinal pains* Gastrointestinal erosion* Gastrointestinal ulcer* Mucositis oesophagitis	Gastrointestinal haemorrhage*			Abdominal complaints Hyperpigmentation of the oral mucosa* Pain or burning sensation
Skin and subcutaneous tissue disorders	Alopecia skin toxicity	Rash/Pruritus Pigmentation of the nails* Skin disorders hyperpigmentation of the skin*	Urticaria* Erythema*			Photosensitivity reaction*
Renal and urinary disorders	Chromaturia*					
Reproductive system and breast disorders	Amenorrhoea			Azoospermia		
General disorders and administration site conditions	General health disorder Fever*	Infusion site erythema chills*	Asthenia			

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)	Not known (Frequency cannot be estimated based on available data)
Investigations	Abnormal transaminase values	Reduced left ventricular ejection fraction				
Injury, poisoning and procedural complications	Chemical cystitis*§					Recall phenomenon*Δ

* Adverse reaction reported following market launch
† Red coloration of urine for 1 to 2 days following use
§ Following intravesical administration
Δ Hypersensitivity of the irradiated skin

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 overdose of epirubicin results in severe myelosuppression (primarily leukopenia and thrombocytopenia), toxic gastrointestinal reactions (predominantly mucositis) and acute cardiac dysfunction.. Latent hear failure has been reported in connection with the use of anthracyclines several months to years after the treatment has been completed (see section 4.4). Patients must be carefully monitored. If signs of heart failure occur, patients should be treated according to the standard guidelines.

Treatment

Symptomatic.
Epirubicin is not amenable to dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Anthracyclines and related substances,
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 cell nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be effective in 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. The efficacy was also proven against human tumours implanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

The pharmacokinetics of epirubicin hydrochloride is linear in the dosage range between 60 and 150 mg/m2. Plasma clearance is not affected by the duration of the infusion or by the treatment schedule.

Distribution
Epirubicin hydrochloride is rapidly and extensively distributed in the tissue following IV administration. The plasma protein binding, primarily albumin, is around 77% and is independent of the concentration. In patients with normal liver and renal function, plasma levels of epirubicin hydrochloride following intravenous administration of 60-150 mg/m² follow a triexponential pattern with a very rapid initial 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 levels and of the metabolic pathway. Distribution studies in rats have shown that epirubicin does not cross the blood-brain barrier. The high plasma clearance values of epirubicin (0.9 l/min) and the slow elimination indicate a high volume of distribution.

Biotransformation
Epirubicin is largely metabolized in the liver.
The most important metabolites identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol. The 4-O-glucuronidation distinguishes epirubicin from doxorubicin and may explain the more rapid elimination of epirubicin and its reduced toxicity. The plasma levels of the most important metabolite, epirubicinol, are always lower than those of the unchanged drug and run practically in parallel.

Elimination
Approximately 9-10% of the administered dose is excreted in the urine within 48 hours. Epirubicin is excreted primarily by the river, approximately

40% of the administered dose is found again in the bile within 72 hours. Hepatic impairment causes higher plasma levels and requires a reduction in the dosage.

Intravesical administration

Pharmacokinetic investigations on patients with carcinoma in situ showed that plasma levels of epirubicin hydrochloride after intravesical instillation of the bladder exceeded 10 ng/ml in one case only. No significant systemic absorption can therefore be assumed. A higher absorption rate is to be expected in patients with lesions of the bladder mucosa (tumour, cystitis, surgery).

Pharmacokinetics in special patient groups

Liver failure
Epirubicin is eliminated by hepatic metabolism and by biliary excretion and the clearance rate is reduced in patients with hepatic impairment. In one study on the effects of liver failure, patients with solid tumours were divided into three groups. The patients in group 1 (n = 22) had AST (SGOT) levels above the upper normal limit (93 IU/l median) and normal serum bilirubin values (0.5 mg/dl median). They received epirubicin hydrochloride doses of between 12.5 and 90 mg/m^2. The patients in group 2 (n = 8) had both altered AST values (175 IU/l median) as well as altered bilirubin values (2.7 mg/dl median) and received epirubicin hydrochloride doses of 25 mg/m^2. The pharmacokinetic parameters were compared with those for patients who had normal serum AST and bilirubin levels and had received epirubicin hydrochloride doses ranging between 12.5 and 120 mg/m^2. The median plasma clearance was reduced by 30% in group 1 and 50% in group 2 compared with patients who had normal liver function. The data from patients with severe liver failure were not evaluated (see sections 4.2 and 4.4.).

Renal failure
No significant changes in the pharmacokinetic parameters of epirubicin hydrochloride or its major metabolite, epirubicinol, were observed in patients with serum creatinine levels < 5 mg/dl (see sections 4.2. and 4.4).

5.3 Preclinical safety data

As with other anthracyclines, epirubicin was mutagenic, genotoxic and carcinogenic in rats.
The main target organs for toxicity after use of epirubicin in animals were the haematopoietic system, the gastrointestinal tract, the skin, the heart, the kidneys, the liver and the reproductive organs. Epirubicin has also proven to be cardiotoxic in rats, rabbits and dogs.
In animal studies, epirubicin was toxic to male and female productive organs. In male rats, the use of epirubicin led to a reduction in the size/weight of the testes and/or the epididymis and reduced spermatogenesis. In female animals,

epirubicin caused major changes to the ovaries and the uterus in rats and atrophy of the uterus in rats and dogs. When used during organogenesis in pregnant rats, epirubicin was embryotoxic and teratogenic, with an observed increased incidence of visceral abnormalities. In rabbits, however, no deformations were observed.
As with other anthracyclines and cytotoxic agents, epirubicin must be considered to be potentially teratogenic.

A local tolerance study in rats and mice showed that extravasations of epirubicin cause tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Water for Injections

Hydrochloric acid for pH adjustment

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 the injection nor any diluted solution should be mixed with any other drugs (a physical incompatibility with heparin has been reported).

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Before first opening: 3 years.

After dilution: after dilution in Glucose 5% or Sodium Chloride 0.9%, chemical and physical in-use stability has been demonstrated for 60 minutes at +25°C.
From a microbiological point of view, the diluted solution 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°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

5ml, 10 ml, 25 ml, 50 ml, 100 ml type I colourless glass vials, with a bromobutyl rubber stopper and flip-off cap. Box of 1, 5 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For methods of administration, see section 4.2.
As with other potentially toxic compounds, caution should be exercised when handling Epirubicin (hydrochloride) 2 mg/ml, solution for injection.
The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundings.
Epirubicin (hydrochloride) 2 mg/ml, solution for injection 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.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom.

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