Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin hydrochloride 2mg/ml, solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
1 ml of solution for injection or infusion contains 2 mg Epirubicin hydrochloride
- 1 vial of 5 ml solution contains 10 mg Epirubicin hydrochloride
- 1 vial of 10 ml solution contains 20 mg Epirubicin hydrochloride
- 1 vial of 25 ml solution contains 50 mg Epirubicin hydrochloride.
- 1 vial of 75 ml solution contains 150 mg Epirubicin hydrochloride.
- 1 vial of 100 ml solution contains 200 mg Epirubicin hydrochloride

Excipient:
1 ml of solution for injection or infusion contains 3.5 mg sodium
- 1 vial of 5 ml solution contains 17.7 mg sodium
- 1 vial of 10 ml solution contains 35.4 mg sodium
- 1 vial of 25 ml solution contains 88.5 mg sodium.
- 1 vial of 75 ml solution contains 265.5 mg sodium.
- 1 vial of 100 ml solution contains 354.1 mg sodium

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epirubicin is used in the treatment of a range of neoplastic conditions including;
- Breast carcinoma
- Gastric carcinoma

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:
- Papillary transitional cell carcinoma carcinoma of the bladder
- Carcinoma in-situ
- Intravesical prophylaxis of recurrence of superficial bladder carcinoma following transurethral resection.

For intravesical use a positive benefit-risk ratio could only be established in patients in whom live attenuated BCG is contra-indicated or inappropriate.

Epirubicin hydrochloride 2 mg/ml can be used in polychemotherapy schedules.

4.2 Posology and method of administration

Epirubicin is only intended for intravenous or intravesical use.

Intravenous use
It is advisable that the red solution, which should be clear and transparent, is injected via the catheter of a free running intravenous infusion of a physiological salt solution or glucose 5% over a period of up to a duration of 30 minutes (depending on the dose and the volume of the infusion). The needle should be properly placed in the vein. This method reduces the risk of thrombosis and extravasation that could lead to severe cellulitis and necrosis.

In case of extravasation, administration should be stopped immediately. Injection in small veins and repeated injection in the same vein can lead to venous sclerosis.

Usual dose
If epirubicin is used as monotherapy, the recommended dose in adults is 60-90 mg/m^2 of body surface area. Epirubicin should be injected intravenously over 3-5 minutes. The same dose is repeated with an interval of 21 days.
With the dosing schedule the haematolo-medullar state of the patient should be taken into account.
If signs of toxicity, including neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose
Epirubicin as monotherapy for the treatment of breast carcinoma with a high dose should be administered in accordance to the following regimen:

For the treatment with a high dose epirubicin can be administered as an intravenous bolus over 3 - 5 minutes or as an infusion up to 30 minutes duration.

Breast carcinoma
In the adjuvant treatment of early breast cancer patients with positive lymph nodes intravenous doses of epirubicin going 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 is recommended.

Lower dose (60-75 mg/m^2 for usual treatment and 105 - 120 mg/m^2 for treatment with high dose) or postponement of the next dose are recommended for patients with reduced bone marrow function due to prior chemotherapy or radiotherapy, due to age or neoplastic bone marrow infiltration. The complete dose per cycle can be distributed over 2 - 3 consecutive days.

The following doses of epirubicin are commonly used in monotherapy and combination therapy for various tumours, as shown:

Cancer indication	**Epirubicin dose (mg/m^2)***	
	Monotherapapy	**Combination therapy**
Gastric cancer	60 - 90	50
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	

* Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination chemotherapy
When Epirubicin hydrochloride 2 mg/ml is used in combination with other antitumoural products, the dose is reduced accordingly. Commonly used doses are shown in the table above.

Special patient groups
Elderly patients
It is recommended to reduce the dose in elderly patients.

Children
The safety and efficacy of epirubicin in children has not been established.

Impaired liver function
The excretion of epirubicin occurs primarily via the liver. In patients with a liver function disorder the dose should be reduced as follows, in order to avoid an increase of general toxicity:

Serum bilirubin	AST (aspartate aminotransferase)	Dose reduction
1.4 – 3 mg/100 ml	2 - 4 times the normal upper limit	Dose reduction of 50%
> 3 mg/100 ml	> 4 times the normal limit	Dose reduction of 75%

Impaired renal function
Moderate renal insufficiency is not a reason for dose reduction, considering the limited amount of epirubicin that is excreted via this route. However, in patients with severe renal insufficiency (serum creatinine > 450 µmol/l) a dose reduction is recommended.

Intravesical use
For instructions on dilution of the product before administration also see section 6.6.

Epirubicin can be administered by intravesical route for the treatment of superficial bladder carcinoma, carcinoma in situ and prophylactic to prevent recurrence after transurethral resection. It should not be administered by intravesical route for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more suitable in these situations.

Various dosing schedules are used. The following can be used as a guideline:
Superficial bladder carcinoma: weekly bladder lavage with 50 mg/50 ml (diluted with a physiological salt solution or sterile water) for 8 weeks. A dose reduction of 30 mg per 50 ml is advised in case of local toxicity (chemical cystitis).
Carcinoma in situ: Up to 80 mg/50 ml (depending on the tolerability of the patient).
Prophylaxis of recurrence after transurethral resection: 4 times a weekly administration of 50 mg/50 ml followed by 11 times a monthly instillation of the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent sterile water for injection or 0.9% sterile saline	Total volume of bladder instillation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be maintained intravesical for 1 - 2 hours. To avoid excessive dilution with urine the patient should be instructed not to drink any fluids within 12 hours before the instillation. During the instillation the patient should be turned every now and then as well as be instructed to urinate at the end of the instillation period.

4.3 Contraindications

Hypersensitivity to epirubicin or any other component of the product, other anthracyclines or anthracenediones.

Lactation

Intravenous use
- persistent myelosuppression
- severe hepatic impairment
- severe myocardial insufficiency (including 4th degree muscular heart failure, acute heart attack and previous heart attack which led to 3rd and 4th degree muscular heart failure, acute inflammatory heart diseases)
- 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
- hematuria
- invasive tumours penetrating the bladder
- catheterisation problems
- large volume of residual urine
- contracted bladder.

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.

Epirubicin must not be administered subcutaneously or intramuscularly.

Initial treatment calls for careful baseline monitoring of various laboratory parameters and cardiac function.

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

Patients should recover from acute toxicities (such as stomatitis, mucositis, 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/m2 every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses (< 90 mg/m2 every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis 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.
It involves a permanent reduction of the QRS-voltage, a prolongation outside the normal limits of the systolic time interval (PEP/LVET) and a reduction of the left ventricular ejection fraction. Early clinical diagnosis of heart failure induced by cytostatic agents appears essential to a successful treatment with digitalis, diuretics, peripheral vasodilators, a diet with a low sodium content and sufficient bed rest. Therefore, cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques.

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 dyspnea, pulmonary edema, dependent edema, 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/m2 or a lower cumulative dose in patients who received radiation of the mediastenal area; 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 (by means of an ECG, echocardiography or nuclear measuring of the ejection fraction (by means of a radionuclide angiography)) 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/m2 epirubicin should be exceeded only with extreme caution.
In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900 - 1000 mg/m2 should only be exceeded with extreme caution with both usual and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly.

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, and concomitant use of other drugs with the ability to suppress cardiac contractility or cardiotoxic drugs (e.g., trastuzumab) (see section 4.5).
Cardiac function monitoring must be particularly strict in patients receiving high cumulative doses and in those with risk factors. Elderly patients, children and patients with a history of heart disease also have a greater risk of cardiotoxicity.
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 leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin hematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia 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 anemia may also occur. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.

Secondary Leukemia - Secondary leukemia, with or without a preleukemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukemia 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 leukemias 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, alkaline phosphatase, ALT 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 patient's pain may be relieved by cooling down the area and keeping it cool for 24 hours. Local infiltration with corticosteroids, with or without the combination of a sodium bicarbonate solution (8.4%) and local application of dimethyl sulfoxide and cold packs have been used with various degrees of success. The patient should be monitored closely during the subsequent period of time, as necrosis may occur after several weeks after extravasation occurs, 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

Tumor-Lysis Syndrome - Epirubicin may induce hyperuricemia because of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumor-lysis syndrome). Blood uric acid levels, potassium, calcium phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-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)

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 (see section 4.6).

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, hematuria, 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 embolization 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.

This medicinal product contains 3.5 mg sodium per ml solution for injection or infusion. To be taken into consideration by patients on a controlled sodium diet.

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 Special warnings and precautions for use).

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 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 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.

Medicinal products that induce the enzyme cytochrome P-450 (such as rifampicin and barbiturates) can increase the metabolism of epirubicin, resulting in a reduction of the efficacy.
Cimetidine 400 mg two times daily given prior to epirubicin 100 mg/m2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter $p<0.05$). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.
Cimetidine 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. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.
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).

Prior administration of higher doses (900 mg/m2 and 1200 mg/m2) of dexrazoxane may increase the systemic clearance of epirubicin resulting and result in a decrease in AUC.

The cardiotoxicity of epirubicin is potentiated by certain radiotherapeutic treatments and by previous or concomitant use of other anthracycline derivatives (e.g. mitomycin-C, dacarbazine, dactinomycin and possibly cyclophosphamide) or other cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes). Epirubicin can potentiate the effect of radiation to the mediastinal area.

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

Concomitant use with ciclosporine, may cause excessive immunosuppression.

4.6 Fertility, pregnancy and lactation

(See section 5.3)

Impairment of 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. Male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment
Epirubicin may cause amenorrhea or premature menopause in premenopausal women.
Women should not become pregnant during treatment with epirubicin. Men and women should use an effective method of contraception during treatment and for 6 months thereafter.

Pregnancy
Experimental data in animals suggest that epirubicin may cause fetal harm when administered to a pregnant woman. If epirubicin is used during pregnancy (particularly in the first trimester) or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the cytostatic drugs should only be used on strict indication and when the potential benefits to the mother have been weight against possible risks of adverse effects on reproduction.

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

Lactation
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.

4.7 Effects on ability to drive and use machines

The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated.
However, epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with epirubicin with the following frequencies: 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 (cannot be estimated form the available data)

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

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Common	Infection
	Not Known	Septic shock (may occur as a result of myelosuppression), sepsis, pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Acute lymphocytic leukemia,acute myelogenous leukemia with or without a pre-leukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 year) latency.
Blood and the lymphatic system disorders	Very Common	Myelosuppression (leukopenia, granucytopenia and neutropenia, anemia and febrile neutropenia)
	Uncommon	Thrombocytopenia
	Not known	Haemorrhage and tissue hypoxia as result of myelosuppression.
Immune system disorders	Rare	Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).
Metabolism and nutrition disorders	Common	Anorexia, dehydration
	Rare	Hyperuricemia (see section 4.4)
Nervous system disorders	Rare	Dizziness
	Not known	Peripheral neuropathy (with high doses), headache
Eye disorders	Not known	Conjunctivitis, keratitis
Cardiac disorders	Rare	Congestive heart failure (see section 4.4), (dyspnoea; oedema, hepatomegaly, ascites, pulmonary oedema, pleural effusions, gallop rhythm) cardiotoxicity (e.g. ECG abnormalities, arrhythmias, cardiomyopathy), ventricular tachycardia,

		bradycardia, AV block, bundle-branch block.
Vascular disorders	Common	Hot flashes, phlebosclerosis
	Uncommon	Phlebitis, thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli (in isolated cases with fatal outcome)
Gastrointestinal disorders	Common	Mucositis (can occur 5 to 10 days after the initiation of the treatment), esophagitis, stomatitis, vomiting, diarrhea which can result in dehydration, nausea (nausea and vomiting often occur within the first 24 hours (in nearly all patients)
Skin and subcutaneous tissue disorders	Very Common	Alopecia (in 60-90% of treated cases. It involves poor beard growth in men. Alopecia is dose-dependent and in most cases reversible)
	Rare	Urticaria, pruritis, local erythematous reactions along the vein that was used for the injection.
	Not Known	Local toxicity, rash, itch, skin changes, erythema, flushes, changes in skin and nail (hyperpigmentation), photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)
Renal and urinary disorders	Very common	Red coloration of urine for 1 to 2 days after administration
	Not known	Proteinuria in patients who were treated with a high dose
Reproductive system and breast disorders	Rare	Amenorrhea, azoospermia
General disorders and administration site conditions	Common	Infusion site erythema
	Rare	Malaise, asthenia, fever, chills, hyperpyrexia
Investigations	Rare	Changes in transaminase levels
	Not Known	Asymptomatic drops in left ventricular ejection fraction
Injury, poisoning and procedural complications	Common	Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4).

Intravesical administration:
As only a small amount of active ingredient is reabsorbed after intravesical instillation, severe systemic adverse drug reactions as well as allergic reactions are rare. Commonly reported are local reactions like burning sensation and frequent voiding (pollakisuria).Occasional bacterial or chemical cystitis have been reported (see section 4.4). These ADRs are mostly reversible.

4.9 Overdose

Acute overdosage with epirubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. During this period a blood transfusion is required as well as isolation in a sterile room. 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 category: Anthracyclines and related substances.
ATC-code: L01DB03

The working mechanism of epirubicin depends on its ability to form complexes with DNA. Experimental studies with cell cultures have shown that epirubicin rapidly penetrates the cell and is recovered in the nucleus where it inhibits the nucleic acid synthesis and the mitosis.

The activity of epirubicin was established on many experimental tumours, amongst which leucaemias L1210 and P388, the sarcoma SA 180 (solid and ascetic form), the B16 melanoma, the breast carcinoma, the lung carcinoma of Lewis and the colon carcinoma 38, furthermore an effect was also shown on human tumours that were transplanted in athymic nude mice (melanoma and mammary, lung, prostate and ovarian carcinoma).

5.2 Pharmacokinetic properties

In patients with a normal liver and kidney function the plasma level of epirubicin drops after an intravenous injection of 60-150 mg/m² in a tri-exponential way with a very rapid first phase and a slow last phase with a mean half life of about 40 hours. These doses fall within the limits of the pharmacokinetic linearity both concerning the plasma clearance values and the metabolism. 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 methods indicate a large distribution volume.

Biotransformation
The most important metabolites that were identified are epirubicinol (13-OH epirubicin), glucuronides of epirubicin and of epirubicinol. The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and can explain the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the most important metabolite, epirubicinol, are always lower than those of the unchanged product and run practically parallel.

Excretion
Approximately 9-10% of the administered dose is excreted via the urine within 48 hours. Epirubicin is primarily excreted via the liver; approximately 40% of the administered dose is recovered in the bile within 72 hours. A liver function disorder causes higher plasma levels and requires a dose reduction.

5.3 Preclinical safety data

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolyphopoietic system, GI tract, kidney, liver and reproductive organs, Epirubicin was also cardiotoxic in rat, rabbit and dog.
Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

Peri/postnatal studies in rat indicate adverse effects on the offspring at clinical doses. It is not known whether epirubicin is excreted in breast milk.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic drugs, epirubicin must be considered potentially teratogenic.

Animal studies indicate that epirubicin has a more favourable therapeutic index and a lower systemic and cardiac toxicity than doxorubicin.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium chloride
hydrochloric acid, for pH adjustment
water for injections

6.2 Incompatibilities

Long-term contact with alkaline solutions should be avoided as this can lead to hydrolysis. Epirubicin hydrochloride 2 mg/ml must not be mixed with heparin due to possible precipitation.

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

6.3 Shelf life

2 years.

Epirubicin hydrochloride 2 mg/ml can be diluted in NaCl 0.9% or Glucose 5% and administered intravenously. For intravesical administration the product should be diluted with NaCl 0.9% or sterile water.
Chemical and physical in-use stability has been demonstrated for 28 days at 15-25°C ± 2°C and at 2 – 8 °C. 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 8°.

6.4 Special precautions for storage

Store in the refrigerator (2-8°C).
Store and transport refrigerated
Do not freeze

For storage conditions of the diluted medicinal product and for storage after opening, see section 6.3.

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to a mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15–25°C)

6.5 Nature and contents of container

Epirubicin hydrochloride 2 mg/ml is delivered in colourless, Type 1 glass vials with bromobutyl rubber cap, aluminium closing and snap-cap, with respectively 5 ml, 10 ml, 25 ml, 75 ml and 100 ml solution for injection or infusion.

Each carton contains a single vial.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

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

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

People working with Epirubicin hydrochloride 2 mg/ml are required to wear protective gloves, safety goggles and a mask.
Epirubicin hydrochloride 2 mg/ml can be diluted in NaCl 0.9% or Glucose 5% and be administered intravenously. The solution must be prepared immediately prior to use.
For intravesical administration the product must be diluted with NaCl 0.9% or sterile water. The concentration of the dilution has to be 0.6-1.6 mg/ml.
Epirubicin hydrochloride 2 mg/ml contains no preservatives and is therefore only suitable for single use. After use the unused remainder should be destroyed according to the regulations for cytostatic agents. See also “Disposal”.

Inactivation of spilled or leaked medicinal product can be obtained with a 1% sodium hypochlorite solution or simply with a phosphate buffering agent (pH >8) until the solution is decolourised. All cleaning materials are disposed of as mentioned under “Disposal”.

Pregnant women must avoid contact with cytostatic agents.

Excreta and vomit should be cleaned up with care.

A damaged vial must be treated with the same precautions and must be considered as contaminated waste. Contaminated waste must be stored in appropriate specially marked waste containers. See under “Disposal”.

Disposal
Any unused product, all materials used in the preparation and administration, or which have come in contact with epirubicin hydrochloride in any way, must be destroyed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.
Swensweg 5
P.O. Box 552
Haarlem, 2003 RN
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA937/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th January 2009

10 DATE OF REVISION OF THE TEXT

February 2012