

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin hydrochloride 2 mg/ml Solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 2 mg of epirubicin hydrochloride.

Each vial of 5 ml contains 10 mg of epirubicin hydrochloride.

Each vial of 25 ml contains 50mg of epirubicin hydrochloride.

Each vial of 50 ml contains 100mg of epirubicin hydrochloride.

Each vial of 100 ml contains 200 mg of epirubicin hydrochloride.

Excipients:

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 25 ml solution contains 88.5 mg sodium.

- 1 vial of 50 ml solution contains 177.0 mg sodium.

- 1 vial of 100 ml solution contains 354.1 mg sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

A red solution

pH of the solution : 2.5 to 3.5.

Osmolarity of the solution: Not less than 275 and not more than 325 milliosmoles/kg H₂O

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Carcinoma of the breast
- Gastric 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 of the bladder
- Intravesical prophylaxis of recurrences 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 for intravenous and intravesical use only.

Intravenous administration:

It is advisable to give the drug via the tubing of a freely running I.V. 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. In case of extravasation, administration should be stopped immediately. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Conventional doses:

When epirubicin is used as a single agent, the recommended dosage in adults is 60 mg/m² to 90 mg/m² body area; the drug should be injected I.V. over 3 minutes to 5 minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

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

High doses:

Epirubicin as a single agent for the treatment of breast carcinoma at high doses should be administered according to the following regimens:

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 cancer

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

Lower doses (60 mg/m² to 75 mg/m² for conventional treatment and 105 mg/m² to 120 mg/m² for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2 to 3 successive days.

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

Cancer indication	Epirubicin Dose (mg/m ²)	
	Monotherapy	Combination Therapy
Gastric cancer ^a	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	

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

Combination therapy

If epirubicin is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function

The major route of elimination of epirubicin is the hepatobiliary system.

In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

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 impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

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 intravesically as a prophylactic agent after transurethral resection of superficial tumours in order to prevent recurrences.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:

8 weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water).

If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.

Carcinoma-in-situ: Up to 80 mg/50 ml (depending on individual tolerability of the patient)

For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at 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 for bladder installation
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 retained intravesically for 1-2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid within 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void at the end of the instillation time.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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
- cardiomyopathy

Intravesical use

- urinary tract infections
- inflammation of the bladder
- haematuria
- 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, neutropenia, thrombocytopenia, and generalized infections) of prior cytotoxic treatment before beginning treatment with epirubicin.

While treatment with high doses of epirubicin (e.g., $\geq 90 \text{ mg/m}^2$ every 3 to 4 weeks) causes adverse events generally similar to those seen at standard doses ($< 90 \text{ mg/m}^2$ every 3 to 4 weeks), the severity of the neutropenia and stomatitis/mucositis may be increased. Treatment with high doses of epirubicin 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 dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Life-threatening CHF is the most

severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The risk of developing CHF increases rapidly with increasing total cumulative doses of epirubicin in excess of 900 mg/m^2 or a lower cumulative dose in patients who received radiation of the mediastinal 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 throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

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

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of $900 - 1000 \text{ mg/m}^2$ 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.

Haematologic Toxicity- As with other cytotoxic agents, epirubicin may produce myelosuppression. Haematologic profiles should be assessed before and during each cycle of therapy with epirubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of epirubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia 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 - Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines, including epirubicin. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiation treatment, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. These 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 patient's pain may be relieved by cooling down the area and keeping it cool for 24 hours. 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.

Tumor-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 alkalinization, 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)

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., urethral obstruction due to massive intravesical tumours).

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. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

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

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

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

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 $\alpha 2b$ 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 when patients have been previously treated with medication which affects the bone marrow (i.e. cytostatic agents, sulphonamides, chloramphenicol, diphenylhydantoin, amidopyrine-derivates, antiretroviral agents).

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 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 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 foetus.

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

There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines. 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* ($\geq 1/10$); *Common* ($\geq 1/100$ to $< 1/10$); *Uncommon* ($\geq 1/1,000$ to $\leq 1/100$); *Rare* ($\geq 1/10,000$ to $\leq 1/1,000$); *very rare* ($\leq 1/10,000$), not known (cannot be estimated from 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, sepsis, pneumonia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Acute lymphocytic leukaemia, acute myelogenous leukaemia
Blood and the lymphatic system disorders	Very Common	Myelosuppression (leucopenia, granulocytopenia 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), allergic reactions following intravesical administration.
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

System Organ Class	Frequency	Undesirable effects
Eye disorders	Not known	Conjunctivitis, keratitis
Cardiac disorders	Rare	Congestive heart failure, (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
	Uncommon	Phlebitis, thrombophlebitis
	Not known	Shock, thromboembolism, including pulmonary emboli
Gastrointestinal disorders	Common	Mucositis, esophagitis, stomatitis, vomiting, diarrhoea, nausea, which can result in loss of appetite and abdominal pain.
Skin and subcutaneous tissue disorders	Very Common	Alopecia
	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, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)

System Organ Class	Frequency	Undesirable effects
Renal and urinary disorders	Very common Not known	Red coloration of urine for 1 to 2 days after administration 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

After the administration of a very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10 days to 14 days. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs

of cardiac failure arise, be treated along conventional lines. Epirubicin is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic Agents – Cytotoxic Antibiotics and Related Substances : Anthracycline 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 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 I.V. injection of 60 mg/m² to 150 mg/m² 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.

In pharmacokinetic studies of patients with carcinoma in situ of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (<10 ng/ml). A significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumour, cystitis, operations), a higher resorption rate can be expected.

Biotransformation

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.

Excretion

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% to 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 within 72 hours. A liver function disorder causes higher plasma levels and requires a dose reduction.

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.

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

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

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.

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

Hydrochloric acid, for pH adjustment

Sodium chloride

Water for Injections

6.2 Incompatibilities

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

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

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

6.3 Shelf life

Unopened container: 18 months

Epirubicin hydrochloride solution for injection or infusion does not contain a preservative or bacteriostatic agent. Vials are, therefore for single use only and any unused portion must be discarded after use.

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

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Keep vial in the outer carton in order to protect from light.

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

Clear, colourless, moulded glass vial (type – I) 5 ml, 25 ml, 50 ml and 100 ml with fluoropolymer coated chlorobutyl rubber stopper and aluminium polypropylene flip off seal.

Pack sizes:

1 x 5 ml vial

1 x 25 ml vial

1 x 50 ml vial

1 x 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Discard any unused solution.

Intravesical administration. Epirubicin should be instilled using a catheter and retained intravesically for 1-2 hour. During instillation, the patient should be rotated to ensure that the vesical mucosa of the pelvis receives the most extensive contact with the solution. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. The patient should be instructed to void at the end of the instillation.

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

Personnel should be trained in good technique for reconstitution and handling.

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

Disposal

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

7 MARKETING AUTHORISATION HOLDER

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