FRESENIUS KABI
caring for life

REVISED SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin Kabi 2 mg/ml Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2 mg/ml Epirubicin Hydrochloride.
25 ml vial contain 50 mg of Epirubicin Hydrochloride.
100 ml vial contain 200 mg of Epirubicin Hydrochloride.

Excipient:
1 ml of solution for injection or infusion contains 3.5 mg sodium
- 1 vial of 25 ml solution contains 88.5 mg sodium.
- 1vial 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 milli osmoles/kg H_2O

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.

4.2 Posology and method of administration

Epirubicin Kabi is for intravenous and intravesical use only.

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

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

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/m^2 to 90 mg/m^2 body area; the drug should be injected I.V. over 3 minutes to 5 minutes and, depending on the patients' 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 monotherapy for the treatment of breast carcinoma with a high doses should be administered according to the following regimens:

For high dose treatment, epirubicin may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

<u>Breast cancer</u>

In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3 weeks to 4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

The drug should be given as an I.V. bolus over 3 minutes to 5 minutes or as an infusion up to 30 minutes. Lower doses (60 mg/m^2 to 75 mg/m^2 for conventional

treatment and 105 mg/m^2 to 120 mg/m^2 for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2 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)[a]**	
	Monotherapy	Combination Therapy
Gastric cancer	60-90	50

[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.

Special patient group
Elderly patients:
It is recommended to reduce the dose in elderly patients

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
For instructions of the product before administration also see section 6.6.

Epirubicin may 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 times 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.

Instructions for administration

Intravenous administration. Epirubicin should be administered into the tubing of a freely flowing intravenous infusion (0.9% sodium chloride or 5% glucose).
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 Kabi 2 mg/ml Solution for Injection are required to wear protective gloves, safety goggles and a mask.

Epirubicin Kabi 2 mg/ml Solution for Injection 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 in any way, must be destroyed in accordance with local requirements.

4.3 Contraindications

Epirubicin Kabi is contraindicated in:

- Hypersensitivity to epirubicin, other anthracyclines/ anthracenediones or to any of the excipients.
- Marked myelosuppression induced by previous treatment with either other antineoplastic agents or radiotherapy.
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
- Current or previous history of cardiac impairment (including New York Heart Association (NYHA) class IV heart failure, acute myocardial infarction and previous infarction with residual NYHA class III or class IV heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences).
- Acute systemic infections
- Severe hepatic impairment
- Severe mucositis of the mouth, pharynx, oesophagus, and gastrointestinal tract.
- Patient who are breast-feeding (see also section 4.6)

For intravesical administration, epirubicin is contraindicated in:

- Urinary tract infections
- Invasive tumours penetrating the bladder
- Catheterisation problems
- Vesical inflammation
- Large volume of residual urine
- Contracted bladder.

4.4 Special warnings and precautions for use

Epirubicin Kabi should be administered only under the supervision of qualified physicians experienced in antiblastic and cytotoxic therapy.

The treatment should preferably take place in centers where they are experienced with these therapies Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of Epirubicin.

Epirubicin must not be administered subcutaneously or intramuscularly. Extravasation of Epirubicin from the vein during injection may cause severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein. In case of extravasation dose occur, the administration via that particular vein is discontinued and resumed at a different site. Local infiltration with corticosteroids, with or without the combination of a sodium bicarbonate solution (8.4%) and local application of dimethyl sulfoxide and packs have been used with various degree of success. If necessary consult a plastic surgeon.

Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with Epirubicin.

If epirubicin is administered as a continuous infusion, this should preferably take place via a central venous catheter. Nausea vomiting and mucositis are often quite severe: administration of appropriate medication is needed.

During each cycle of treatment with Epirubicin, patients must be carefully and frequently monitored. Red and white blood cells, neutrophils and platelet counts should be carefully assessed both before and during each cycle of therapy. Leukopenia and neutropenia are usually transient with conventional and high-dose schedules, reaching a nadir between the 10th and 14th day and returning to normal values by the 21st day; they are more severe with high dose schedules. Anaemia and thrombocytopenia are also of a passing nature and occur according to the same pattern. Very few patients, even receiving high doses, experience thrombocytopenia (< 100,000 platelets/mm^3).

Patients must have adequately recovered from severe stomatitis or mucositis before starting treatment with Epirubicin.

Epirubicin is primarily eliminated via the liver. Therefore, it is necessary to evaluate the liver function (AST, ALT, alkaline phosphatase, bilirubin) prior to the treatment and again during the treatment. In patients with an elevated bilirubin level or AST the epirubicin clearance can be delayed, which can lead to an increase of the general toxicity. For these patients a dose reduction is recommended (see also section 4.2). Patients with a severe liver function disorder should not use epirubicin (see also section 4.3).

In patients with a reduced renal function the serum creatinine level should be monitored regularly prior to and during the treatment. For patients with increased serum creatine (>450 µmol/l) it is recommended to reduce the dose (see also section 4.2).

Heart failure can occur, particularly in patients who were administered a cumulative dose of 900 mg/m^2, or a lower cumulative dose in patients who received radiation of the mediastenal area. With cumulative doses <900 mg/m^2, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with epirubicin should be discontinued. Prior therapy with related anthracyclines, such as doxorubicin or daunorubicin or anthracenedion derivatives, should also be taken into account with

the total administered dose of epirubicin. Elderly patients, children and patients with a history of heart disease also have a greater risk of cardiotoxicity.

In establishing the maximal cumulative doses of Epirubicin, any concomitant therapy with potentially cardiotoxic drugs should be taken into account. A cumulative dose of 900 mg/m^2 to 1000 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses. Above this level the risk of irreversible congestive cardiac failure increases greatly.

An ECG is recommended before and after each treatment cycle Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses <900 mg/m^2, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of cardiac failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with Epirubicin should be discontinued.

Cardiomyopathy induced by anthracyclines, is associated with a persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the left ventricular ejection fraction. Early clinical diagnosis of heart failure induced by cytostatic agent appear essential to a successful treatment with digitalis, diuretic, peripheral vasodilators a diet with a low sodium diet content and sufficient bed rest.

Cardiac monitoring of patients receiving Epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques such as ECG, Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of Epirubicin at the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multigated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increase cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

Heart failure may appear several weeks after discontinuing therapy with Epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area and/or who are under medical treatment with potentially cardiotoxic medicinal products (see Section 4.5).

As other cytotoxic agents, Epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that

this phenomenon may be recognised and properly managed. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumorlysis syndrome.

Epirubicin may impart a red colour to the urine for 1 day to 2 days after administration.

Both men and women must use effective contraceptive measures, both during and for 6 months after the treatment. Men who have a desire to father children should be informed about the possibility of cryopreservation (see also section 4.6).

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 interaction

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon α2b, paclitaxel and quinine.

Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

Prior administration of higher doses (900 mg/m^2 and 1200 mg/m^2) 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.

The co-administration of interferon α2b may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. Paclitaxel has been shown to increase plasma concentrations of epirubicin when paclitaxel is administered before epirubicin. When paclitaxel is administered after epiribucin no detecable changes in epirubicin plasma concentrations have been observed. With concomitant use, the latter administration schedule is therefore recommended.
In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.

One study has shown that paclitaxel clearance is reduced by 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.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m^2 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-deoxydoxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.

Epirubicin used in combination with other cytotoxic agents may result in additive myelotoxicity.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medications, which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, 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.

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.

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.

Epirubicin is mainly metabolised in the liver; each concomitant medication which affects hepatic function can also affect the metabolisation or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity.

This product is generally not recommended in combination with live attenuated vaccines because of risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis)

Concomitant use with ciclosporine may cause excessive immunosuppression.

4.6 Pregnancy and lactation

Fertility

Epirubicin can have genotoxic effects. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.

Women should not become pregnant during treatment with epirubicin. Men and women should use an effective method of contraception during treatment and for six months thereafter.

Pregnancy

Epirubicin is a potential teratogen and if administered to pregnant women may cause miscarriage, embryotoxicity and foetal death. During pregnancy, particularly the first trimester, 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. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during epirubicin therapy, and use effective contraception during treatment with epirubicin.

Breast-feeding

It is unknown whether epirubicin is excreted in human breast milk. A risk to the breastfeeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with epirubicin.

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

Adverse event frequencies have been categorised as follows:
Very common (≥1/10);
Common (≥1/100, <1/10);
Uncommon (≥1/1,000, <100);
Rare (≥1/10,000, <1/1,000);
very rare (<1/10,000),
not known (cannot be estimated from the available data).

Within every frequency group the side effects are arranged according to reducing severity.

Treatment with epirubicin often causes side effects, some of which are severe. Careful observance of the patient is therefore needed. The frequency and the nature of the side effects are influenced by the rate of administration and the dose. Bone marrow depression (usually temporary in nature) and cardiotoxicity are acute dose limiting side effects.

Investigations
Rare Increased transaminase levels have been reported.

Cardiac disorders:
Rare: Cardiotoxicity (ECG changes, tachycardia, arrhythmia (T-top flattening, ST- segment depression), cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusions, gallop

rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block (see Section 4.4).

The risk of developing congestive heart failure increases with the total cumulative dose of epirubicin and with previous therapy with related anthracyclines such as doxorubicin, daunorubicin or anthracene derivatives. Elderly patients and children are at increased risk for developing cardiomyopathy. Patients with a history of heart diseases also have a greater risk of cardiotoxicity. Patients must be observed carefully and should be treated conventionally at the first signs of heart failure. (See also section 4.4).

Blood and the lymphatic system disorders:

Very common: Myelosuppression (leucopenia, granulocytopenia, neutropenia, febrile neutropenia, anaemia). Haemorrhage and tissue hypoxia (as a result of myelosuppression) may occur. High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and has caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (< 500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients.Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Common: Thrombocytopenia

Gastrointestinal disorders:

Common Mucositis can occur 5 to 10 days after the initiation of the treatment and usually involves stomatitis with painful erosions, frequently across the entire side of the tongue and on the sublingual mucosa. Nausea'and vomiting often occur within the first 24 hours (in nearly all patients), diarrhoea which can result in dehydration, anorexia, loss of appetite, abdominal pain.

Rare Oesophagitis. Hyperpigmentation of the oral mucosa also occured.

Renal and urinary disorders:

Very common: Chromaturie (urine red coloured Proteinuria has been reported in patients who were treated with a high dose.

Skin and subcutaneous tissue disorders:

Very common: Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.

Common: Hot flushes, Extravasation can lead to severe cellulitis, blister formation and local tissue necrosis, which requires surgical measures (including skin transplantation). The

risk can be reduced by following the correct administration method (via a fast-running infusion).

Uncommon: Hyperpigmentation of skin and nails. Skin reddening.

Rare: Urticaria.

Infections and infestations:

Frequency unknown: Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression.

Injury, poisoning and procedural complications:

Common: Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration.

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: Secondary acute myeloid leukaemia with or without a preleukaemic phase, in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemias have a short (1-3 year) latency.

Vascular disorders:

Common Redness along the infusion vein, local pain. Local phlebitis, phlebosclerosis

Uncommon: Thrombophlebitis

Frequency unknown: Coincidental cases of thromboembolic events (including pulmonary embolism [in isolated cases with fatal outcome]) have occurred.

General disorders and administration site conditions:

Common: Local reactions (chemical cystitis, sometimes haemorrhages) can occur with intravesical administration.

Uncommon: Headache

Rare: Fever, chills, dizziness, hyperuricaemia (as a result of rapid lysis of neoplastic cells). Hyperpyrexia, malaise and weakness have also been reported.

Immune system disorders:

Common: Allergic reactions following intravesical administration.

Uncommon: Sensitivity to light or hypersensitivity in the case of radiotherapy (“recall phenomenon”).

Rare: Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).

Nervous system disorders:

Effects on the nervous system, such as headache, dizziness and peripheral neuropathy (with high doses) have been reported.

Reproductive system and breast disorders:

Rare: Amenorrhea, azoospermia.

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/m^2 to 150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway.

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

It is not recommended that Epirubicin Kabi 2 mg/ml Injection be mixed with other medicinal products. However, Epirubicin can be used in combination with other anticancer drugs.
Contact with solutions of alkaline pH should be avoided since it causes hydrolysis of the medicinal product. Epirubicin should not be mixed with heparin due to chemical incompatibility causing precipitation.

6.3 Shelf life

Unopened container: 18 months

After first opening of the container: The vials are 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) 25 ml and 100 ml with fluoropolymer coated chlorobutyl rubber stopper and aluminium polypropylene flip off seal.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

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

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 Kabi 2 mg/ml Solution for Injection are required to wear protective gloves, safety goggles and a mask.

Epirubicin Kabi 2 mg/ml Solution for Injection 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 in any way, must be destroyed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

Revised: February 2009