Public Assessment Report

Mutual Recognition Procedure

EPIRUBICIN HYDROCHLORIDE 2 MG/ML SOLUTION
FOR INJECTION OR INFUSION

UK/H/1509/001/E01

UK Licence No: PL 18727/0008

FRESENIUS KABI ONCOLOGY PLC
LAY SUMMARY

On 25th September 2007, the UK granted Fresenius Kabi Oncology PLC a national Marketing Authorisation (licence) for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion.

On 13th March 2009, Fresenius Kabi Oncology PLC was granted a Marketing Authorisation (licence) in Austria, Germany, Denmark, Greece, Spain, Finland, Hungary, Ireland, Italy, the Netherlands, Poland and Sweden, via a mutual recognition procedure.

On 31st December 2010, Fresenius Kabi Oncology PLC was granted a Marketing Authorisation (licence) in Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Romania, the Slovak Republic and Slovenia, via a second wave mutual recognition procedure.

The active ingredient in this medicine is epirubicin hydrochloride.

Epirubicin belongs to the therapeutic group of antineoplastic agents (medicine against cancer). It is used either alone or in combination with other anti-cancer medicines.

Epirubicin is used in the treatment of:
- Breast cancer
- Stomach cancer

Epirubicin is also used intravesically to treat early (superficial) urinary bladder cancer and help prevent recurrence of bladder cancer after surgery.

Epirubicin is often used concomitantly with other cancer fighting medicinal products (in so-called polychemotherapy schedules).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion outweigh the risks and a Marketing Authorisation was granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about licence procedures</th>
<th>Page 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Patient Information Leaflets</td>
<td>Page 16</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 19</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 21</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after repeat-wave MRP procedure</td>
<td>Page 30</td>
</tr>
</tbody>
</table>
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Epirubicin hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Injection or Infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>2 mg/ml</td>
</tr>
</tbody>
</table>
| **MA Holder** | Fresenius Kabi Oncology PLC  
Lion Court, Farnham Road  
Bordon, Hampshire  
GU35 0NF  
United Kingdom |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | UK/H/1509/001/MR: Austria (AT), Germany (DE), Denmark (DK), Greece (EL), Spain (ES), Finland (FI), Hungary (HU), Ireland (IE), Italy (IT), the Netherlands (NL), Poland (PL) and Sweden (SE)  
UK/H/1509/001/E01: Belgium (BE), Bulgaria (BG), Cyprus (CY), Czech Republic (CZ), Estonia (EE), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), Norway (NO), Portugal (PT), Romania (RO), the Slovak Republic (SK) and Slovenia (SI) |
| **Procedure Number** | UK/H/1509/001/E01 |
| **End of Procedure** | Day 90 – 17th November 2010 |
Module 2
Summary of Product Characteristics

Please note that the SmPC, PIL and labelling shown are the versions which were approved at Day 90 of the repeat-wave MR procedure. Subsequent variations to the SmPC, PIL and labelling have been approved since the end of the procedure (please see module 6 at the end of this report).

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion.

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.
- 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 milli osmoles/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.

4.2 Posology and method of administration

Epirubicin 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/m² to 90 mg/m² 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 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.

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.

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/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:

<table>
<thead>
<tr>
<th>Cancer indication</th>
<th>Epirubicin Dose (mg/m²)²</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>60-90</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

² 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**

<table>
<thead>
<tr>
<th>Dose Epirubicin required</th>
<th>Volume of 2 mg/ml Epirubicin injection</th>
<th>Volume of diluent sterile water for injection or 0.9% sterile saline</th>
<th>Total volume for bladder installation</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>15 ml</td>
<td>35 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>50 mg</td>
<td>25 ml</td>
<td>25 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>80 mg</td>
<td>40 ml</td>
<td>10 ml</td>
<td>50 ml</td>
</tr>
</tbody>
</table>

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**
For instructions before administration, also see section 6.6.

**4.3 Contraindications**

Epirubicin 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 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 extravasation does 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. Leucopenia 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/mm³).

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/m², or a lower cumulative dose in patients who received radiation of the mediastenal area. With cumulative doses <900 mg/m², 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/m² to 1000 mg/m² 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/m², 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 multi-gated 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 increased 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 alkalisation 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/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.

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 epirubicin no detectable 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/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-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 the haematopoiesis needs to be kept in mind with a (pre-) treatment with medications, which influence the bone marrow (i.e. cytostatic agents, sulfonamide, 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 metabolism 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 weighed 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* ($\geq 1/10$);

*Common* ($\geq 1/100, < 1/10$);

*Uncommon* ($\geq 1/1,000, < 100$);

*Rare* ($\geq 1/10,000, < 1/1,000$);

*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 occurred.

Renal and urinary disorders:
PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion

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 dose 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

It is not recommended that Epirubicin Hydrochloride 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 Hydrochloride 2 mg/ml Solution for Injection or Infusion are required to wear protective gloves, safety goggles and a mask.
Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion 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.

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7. MARKETING AUTHORISATION HOLDER

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

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

< To be completed nationally>
Module 3
Patient Information Leaflet

PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion
UK/H/1509/001/E01

In this leaflet:
1. What Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is and what it is used for
2. Before you use Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion
3. How Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is given
4. Possible side effects
5. How to Solve Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion
6. Further Information

1. WHAT EPIRubicin HYDROCHLORIDE 2 MG/ML SOLUTION FOR INJECTION OR INFUSION IS AND WHAT IT IS USED FOR
Epirubicin belongs to the therapeutic group of anthracyclines (medicines that target cancer). Epirubicin makes sure that cancer cells cannot grow any more, which eventually kills them. It is used either alone or in combination with other anti-cancer medicines.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is used in the treatment of:
- Breast cancer
- Stomach cancer

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is also used intravenously to treat early (superficial) urinary bladder cancer and help prevent recurrence of bladder cancer after surgery.

2. BEFORE YOU USE EPIRubicin HYDROCHLORIDE 2 MG/ML SOLUTION FOR INJECTION OR INFUSION
Do not use Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion:
- If you are allergic (hypersensitive) to epirubicin or any of the other ingredients of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion or to any other similar medicines (belonging to a group of medicines called anthracyclines) (e.g. doxorubicin and daunorubicin or adriamycin)
- If you have fewer blood cells than normal caused by previous treatment with other antitumor drugs or by previous radiotherapy. Your doctor will check this.
- If you have been treated with the maximum dose of some other anti-cancer medicines including daunorubicin and doxorubicin which belong to the same group of drugs as eprubicin (called anthracyclines). These medicines have similar side effects (including those effects on the heart).
- If you have had surgery or chemotherapy or radiation therapy within the last 14 days.
- If you have an acute severe infection.
- If you have severe liver problems
- If you have severe inflammation of the mouth, throat, gut, and intestinal tract
- If you are breast feeding.

When administered intravenously (directly into the bladder), do not use eprubicin:
- If the kidney has been affected by cancer or it has been affected by other diseases and the dose is not adjusted
- If you have an infection in your urinary tract
- If you have pain or inflammation in your bladder
- If your doctor has problems inserting a catheter (tube) into your bladder
- If there is a large volume of urine left in your bladder after you attempt to empty it.
- If you have a contracted bladder.

Take special care with Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion:
- to ensure the numbers of white and red blood cells and platelets do not drop too low. Your doctor will regularly check this.
- If you are experiencing severe inflammation or ulcers in your mouth.
- To check the level of uric acid in your blood. Your doctor will check this.
- If your liver and kidneys are not working properly. This may cause an increase in side effects. Both the kidney function and the liver function will be checked regularly and if needed the dose will be adjusted.
- To ensure your heart is working properly. The dose of eprubicin will have to be adjusted. Your doctor will regularly check this.
- If you have received or are receiving radiotherapy to the chest area or are receiving medications that might have side effects on your heart.
- If you notice a sensation of discomfort close to or at the injection site during the infusion (possible leakage in the surrounding tissue). Tell your doctor immediately.
- If you have had children. Both men and women should use effective contraceptive measures both during and for 6 months after the use of this medicine to prevent pregnancy.
- If you are elderly or a child, because of the higher risk of severe cardiac side effects. Your cardiac function will be checked before and after the treatment with eprubicin.

If you have previously been treated with products to fight cancer (such as with doxorubicin or daunorubicin or anthracyclines derivatives) or if you have had radiation, because the risk of severe cardiac side effects is greater. Inform your doctor because this is included in determining the total dose of eprubicin you will be administered.

If you suffer from infections or bleeding. Epirubicin may affect the bone marrow. The number of white blood cells in your blood will be reduced, which makes you more susceptible to infections (neutropenia). Bleeding can occur more easily (thrombocytopena). These side effects are temporary in nature. The reduction of the number of white blood cells is greatest 10-14 days after the administration and usually returns to normal 21 days after the administration.

If you have recently received or want to receive any vaccination, or to the level of uric acid in your blood. Your doctor will check this product may impart red colour to the urine.

Please consult your doctor if one of the above mentioned warning is applicable to you, or has been applicable to you in the past.

Taking other medicines:
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Special care will be taken if you are using any of the following medicines:
- other medicines that may affect your heart, for example other medicines against cancer (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes, mitomycin-C, dacarbazine, and dacarbazine). Calcium channel blockers (used to control high blood pressure, chest pain, and irregular heart beat), the betablockers to the heart can increase. Extra monitoring of the heart is generally necessary. Caution should be taken in the administration. Epirubicin can increase the effect of radiation and even after quite some time after the radiation it can cause serious side effects in the irradiated area.
- other medicines that may affect your liver, e.g. barbiturates (used to treat epilepsy) or anticoagulants (used to treat blood clots). These products decrease the amount of eprubicin in the blood, which could lead to a reduced effect of eprubicin.
- other medicines that may affect the bone marrow, e.g. other cancer treatments, sulfonamides, chloramphenicol (used to treat infection), diphenylhydantoin (used to treat epilepsy), amphotericin (used to relieve pain), antitumor agents (used to treat HIV-infection), the formation of blood cells can be disturbed.
- co-induces (a drug used to reduce the acid in your stomach); the amount of eprubicin in the blood is increased, which could lead to an increase of the side effects.
- paclitaxel and docetaxel (drugs used in some cancers); when paclitaxel is administered immediately after eprubicin, the amount of eprubicin in the blood is increased, which could lead to an increase of the side effects.
- interferon alfa-2b (a drug used in some cancers and liposomes and for some forms of hepatitis)
- quinine (a drug used for treatment of malaria and for leg cramps); quinine may speed up the distribution of eprubicin into the body, which may have a negative effect on the red blood cells.
- doxorubicin (a drug sometimes used with docetaxin to reduce the risk of heart problems) the time that eprubicin is present in the body may be increased, which could lead to a decreased effect of eprubicin.
- desmopressin (a drug used to treat some rare conditions), when used together eprubicin may have a negative effect on bone marrow.
-Live attenuated vaccines; there is risk of fatal disease therefore this combination is not recommended.
- Products that cause heart failure.
- Products that influence the liver function; the degradation of eprubicin by the liver may be increased, which may cause a reduced effect of eprubicin or an increase of the side effects.
- Ciclosporine (a product that suppresses the immune system), the immune system may be suppressed too much.

Please tell your doctor or pharmacist if you are using or have recently used any other medicine, including medicines obtained without a prescription.

Using eprubicin with food and drink:
You should not drink within 12 hours before application when eprubicin will be administered in the bladder.

Pregnancy and Breast-Feeding:
Please tell your doctor or pharmacist if you are pregnant or are planning to become pregnant.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is not recommended during pregnancy. There are no adequate and well-controlled studies in pregnant women. If the use of this medicine is considered necessary, the anticipated benefit must be carefully weighed against the potential risk to the unborn child. If this medicine is used during pregnancy or if the mother is exposed to eprubicin during pregnancy, the infant may be at risk for harm.

Breast-feeding:
Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is not recommended during breastfeeding. There are no adequate and well-controlled studies in nursing women. If the use of this medicine is considered necessary, the anticipated benefit must be carefully weighed against the potential risk to the nursing infant. The infant may be at risk for harm.

Please tell your doctor or pharmacist if you are taking any other medicine together with eprubicin.

Driving and using machines:
No studies on the effects on the ability to drive and use machines have been performed. The effect may be different in different people. If you have a history of liver disease, alcoholism, or are taking other medicines that may affect liver function, a careful evaluation of these effects is necessary. The use of this medicine is not recommended during breastfeeding. If your doctor has recommended this medicine for you during breastfeeding, do not breastfeed until your doctor has determined it is safe to do so. If you are breastfeeding, this medicine may enter your breast milk. If this medicine is necessary for you during breastfeeding, it must be used under close medical supervision. The decision to use this medicine during breastfeeding must be carefully weighed against the potential risk to the nursing infant. If this medicine is used during pregnancy or if the mother is exposed to eprubicin during pregnancy, the infant may be at risk for harm.

Anaphylactic shock could occur if you are allergic to eprubicin or any of the other ingredients of eprubicin. If this occurs, stop using eprubicin and seek emergency medical attention immediately. If you have an allergy to eprubicin or any of the other ingredients of eprubicin, you should not use eprubicin.
PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion UK/H/1509/001/E01

performed with epirubicin. However, epirubicin may cause nausea and vomiting, which can temporarily affect your ability to drive and use machines.

Important information about some of the ingredients of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion:
This medicinal product contains 3.5 mg of sodium per ml of solution for injection. This may cause an adverse effect on your health if you are sensitive to sodium or have kidney disease.

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

3. HOW EPIRUBICIN HYDROCHLORIDE 2 MG/Ml SOLUTION FOR INJECTION OR INFUSION IS GIVEN
Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion will only be given to you by a doctor who specialises in this type of treatment. Before and during treatment with Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion, your doctor will discuss the pros and cons of the treatment with you, taking into account your general health, your body weight, your sex, your age, your kidney function, and any other medications you may be taking.

When given by injection or infusion into a vein:
Each dose of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion will be based on your body surface area. This is calculated from your height and weight. The dose of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion given to you will depend on the type of cancer you have, your body weight, your age, your kidney function, and any other medications you may be taking.

When given as a single agent, the usual dose is 60-80 mg/m² body surface area. This dose is administered as a single dose or divided over 2 to 3 consecutive days. This is repeated every 21 days. In combination with other cancer medicines the dose is reduced. Higher doses (100-120 mg/m² body surface area) may be given to you if you suffer from breast cancer.

Dosage will be reduced on the following dose should be delayed if you have a low level of white blood cells in your body. If you are elderly, you have liver problems, or if the drug is used in combination with other antitumor drugs.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion may be given as an injection into a vein over 2 to 3 minutes. It may also be diluted with glucose (sugar) solution or sodium chloride (salt water) before it is infused slowly, usually via a drip into a vein over 30 minutes. Usually it will be given to you every 3 (or 4) weeks.

The needle must remain in the vein while Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is being given. If the needle comes out or becomes loose, or if the solution is going into the tissue outside the vein (you may feel discomfort or pain), tell the doctor or nurse immediately.

When given directly into the bladder (intravesical administration):
The medicine may be given directly into the bladder using a catheter. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much.

The dose will depend upon the type of bladder cancer.

The solution should be kept in your bladder for 1 to 2 hours after instillation. You will be rotated occasionally to ensure even exposure of all parts of the bladder to the drug.

Care should be taken to ensure that the contents of the bladder (urine) are not emptied until at least 1 hour after the instillation.

If you receive more Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion than you should:

Because this medicine is administered by medical personnel, an overdose is unlikely. Immediately contact your doctor if you suspect that too much Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion has been administered.

An overdose of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion may cause a decrease in the number of your red and white blood cells. It may also cause serious heart problems as can occur for up to 6 months after the overdose. If you received an overdose, your doctor will carefully monitor you and, if necessary, start the required treatment.

If you missed a dose of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion:

Because this medicine is administered by medical personnel it is unlikely that a dose is missed.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion needs to be given on a fixed schedule. Be sure to keep all appointments. If you miss a dose, you should discuss this with your doctor. Your doctor will decide when you should be given your next dose of Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion.

If you stop treatment with Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion:

Stopping your treatment with Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion may stop the effect on tumour growth. Do not stop treatment with Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion unless you have discussed this with your doctor.

If you notice that Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion is too strong or too weak, consult your doctor or pharmacist.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, epirubicin can cause side effects, although not everybody gets them.

If any of the following happen when epirubicin is given into a vein, tell your doctor immediately:
any redness, pain or swelling at the injection site. Tissue damage may occur after accidental injection outside the vein
symptoms of heart problems such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with epirubicin)
severe allergic reaction, symptoms include dizziness, skin rash, itching, fever, chills, swelling of the face and difficulty in breathing of wheeze. In some cases collapse may occur.

These are very serious side effects. You may need urgent medical attention.

The following side effects may also occur:

Side effects may appear very common (in more than 1 in 10 patients);
uncommon (in more than 1 in 100, but less than 1 in 10 patients);
very rare (in less than 1 in 10,000 patients);
not known (cannot be estimated from the available data).

Very common:
- inhibition of bone marrow production (myelosuppression)
- decreased number of white blood cells (leucopenia)
- increased number of a special form of white blood cells (granulocytopenia and neutropenia)
- leucopenia accompanied by fever (febrile neutropenia)
- increased number of red blood cells (anaemia)
- bleeding (haemorrhage) and tissue hypoxia (inadequate oxygen supply) as a result of myelosuppression
- heart failure (atrioventricular) normally reversible
- lack of breast growth in males
- your urine may have a red colour for up to two days after treatment. This is normal and nothing to worry about.

Common:
- allergic reactions
- feeling sick (nausea)
- being sick (vomiting)
- diarrhoea
- feeling very dry and thirsty (dehydration)
- loss of appetite
- abdominal pain
- hot flashes
- inflammation of the mucosa of the mouth with areas of painful erosions, ulceration and bleeding (stomatitis), inflammation of a mucous membrane (mucositis)
- redness along the infusion vein, local vein inflammation (phlebitis)
- thickening of the vein walls (veno-occlusive disease)
- bladder inflammation with pain when passing urine (chemical cystitis), sometimes with blood in the urine (haemorrhagic) following administration into the bladder
- headache, dizziness (disorientation), injury or peripheral nerves characterised by a creeping sensation, numbness and/or pain in hands and/or feet (peripheral neuropathy).

If epirubicin leaks outside the vein (extravasation) it may lead to a severe inflammation of the subcutaneous connective tissue (collateral), blister formation and local tissue death.

Uncommon:
- decreased number of platelets (thrombocytopenia)
- sensitivity to light or hyperpigmentation in the case of radiotherapy
- venin inflammation related to a blood clot (thrombophlebitis)
- increased pigmentation (hyperpigmentation) of skin and nails
- skin reddening

Rare:
- severe hypersensitivity (anaphylaxis) with or without shock including skin rash, pruritus (itching), fever and chills
- ECG-changes
- rapid heart rate (tachycardia)
- slow heart rate (bradycardia)
- special forms of arrhythmia (AV block and bundle-branch block)
- third heart sound (gallop rhythm)
- heart muscle disease (cardiomyopathy)
- difficulty in breathing (dyspnoea)
- accumulation of fluid (oedema)
- enlargement of the liver
- accumulation of fluid in the abdominal cavity (ascites)
- lung oedema
- accumulation of fluid between thorax and lung (pleural effusions)
- urticaria (hives)
- chills
- dizziness
PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion  UK/H/1509/001/E01

The following information is intended for medical and healthcare professional only.

PREPARATION GUIDE FOR USE WITH EPIRUBICIN HYDROCHLORIDE 2 MG/ML SOLUTION FOR INJECTION OR INFUSION

It is important that you read the entire contents of this procedure prior to the preparation of either the Epirubicin Hydrochloride 2 mg/ml Solution for injection or Infusion.

1. FORMULATION
Epirubicin Hydrochloride 2 mg/ml solution for injection or infusion.
Excipients:
- sodium chloride
- hydrochloric acid, for pH adjustment
- water for injections

2. PRESENTATION
Store in the refrigerator (2–8°C). Do not freeze.

Storage of the solution for injection at refrigerated conditions can result in the formation of a gelated product. This gelated 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).

2.1 Epirubicin hydrochloride vial:
- 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.

3. RECOMMENDATIONS FOR THE SAFE 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 Solution for Injection or Infusion are required to wear protective gloves, safety goggles and a mask.

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion contains no preservatives and is therefore only suitable for single use. After the unsealed remainder should be destroyed according to the regulations for cytotoxic 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 cytotoxic 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".

4. PREPARATION OF THE SOLUTION
Epirubicin is only intended for intravenous or intravascular use.

4.1 PREPARATION FOR THE INTRAVENOUS ADMINISTRATION

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 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.

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.

4.2 PREPARATION FOR THE INTRAVASCULAR ADMINISTRATION

<table>
<thead>
<tr>
<th>Dose Epirubicin (mg)</th>
<th>Volume of 2 mg/ml Epirubicin injection (ml)</th>
<th>Volume of diluent sterile water for injection or 0.9% sterile saline (ml)</th>
<th>Total volume for bladder instillation (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>15</td>
<td>35</td>
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<td>80</td>
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<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

5. 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.
Module 4
Labelling

Each vial contains 50 mg epirubicin hydrochloride.
Also contains hydrochloric acid, sodium chloride and water for injections.

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

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

For single use only.
Read the package leaflet before use.

Cytotoxic Agent. Discard any unused solution.
For appropriate disposal, refer the package leaflet.

Pantone 7495 C
Pantone 285 C
Pantone 300 C
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
A Marketing Authorisation was granted via a National Procedure for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion in the UK on 25th September 2007.

A Marketing Authorisation via a Mutual Recognition Procedure for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion was granted in Austria, Germany, Denmark, Greece, Spain, Finland, Hungary, Ireland, Italy, the Netherlands, Poland and Sweden on 13th March 2009 (UK/H/1509/001/MR).

Based on the review of the data on quality, safety and efficacy, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Latvia, Lithuania, Luxembourg, Malta, Norway, Portugal, Romania, the Slovak Republic, Slovenia and the UK (reference member state) considered that the application for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion could be approved via the Mutual Recognition Procedure (repeat-wave) on 31st December 2010 (UK/H/1509/001/E01).

This prescription only medicine (POM) is used in the treatment of a range of neoplastic conditions including;
• Carcinoma of the breast
• Gastric cancer

When administered intravesically, the product 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.

This application for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion was submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Pharmorubicin Solution for Injection 2mg/ml, approved in the UK to Farmitalia Carlo Erba Limited on 18th January 1991.

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.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known drug substance. The pharmacology of epirubicin hydrochloride is well-established. No clinical studies have been performed and none are required for these applications as the proposed product is an aqueous solution at the point of administration and contains the same concentration of drug substance as the already approved reference product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A Risk Management Plan has not been submitted and one is not required for an application of this type.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Epirubicin hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anthracycline and Related Substances (L01D B03)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>2 mg/ml Solution for Injection or Infusion</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1509/001/E01</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom (UK)</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>UK/H/1509/001/MR: Austria (AT), Germany (DE), Denmark (DK), Greece (EL), Spain (ES), Finland (FI), Hungary (HU), Ireland (IE), Italy (IT), the Netherlands (NL), Poland (PL) and Sweden (SE)</td>
</tr>
<tr>
<td></td>
<td>UK/H/1509/001/E01: Belgium (BE), Bulgaria (BG), Cyprus (CY), Czech Republic (CZ), Estonia (EE), Latvia (LV), Lithuania (LT), Luxembourg (LU), Malta (MT), Norway (NO), Portugal (PT), Romania (RO), the Slovak Republic (SK) and Slovenia (SI)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18727/0008</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Fresenius Kabi Oncology PLC</td>
</tr>
<tr>
<td></td>
<td>Lion Court, Farnham Road</td>
</tr>
<tr>
<td></td>
<td>Bordon, Hampshire</td>
</tr>
<tr>
<td></td>
<td>GU35 0NF</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

S.  Drug substance

INN:  Epirubicin hydrochloride

Chemical name:  \((8S,10S)\)-10-\([\text{3-amino-2,3,6-trideoxy-a-L-arabino-hexopyranosyl}]\)oxy\()-6,8,11\)-trihydroxyl-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

Structural formula:

![Structural formula of Epirubicin hydrochloride](image)

Molecular formula:  \(C_{27}H_{29}NO_{11},\ HCl\)

Molecular weight:  579.99

Appearance:  An orange-red crystalline powder

Solubility:  soluble in water and in methanol, slightly soluble in ethanol and practically insoluble in acetone

Epirubicin hydrochloride complies with its European Pharmacopoeia monograph.

The manufacturer of the drug substance holds a valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificate of Suitability. The quality of the substance is suitably controlled in line with the current edition of the relevant European Pharmacopoeia Monograph.

All aspects of the manufacture of the active substance from its starting materials were assessed in relation to the approval of the Certificate of Suitability.

All potential known impurities have been identified and characterised.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference and impurity standards used. Batch analysis data are provided and comply with the proposed specification.

The container closure system and stability of the drug substance complies with information given in the Certificate of Suitability. The re-test period was assessed in relation to the approval of the Certificate of Suitability and is satisfactory.
P.  Medicinal Product

Other Ingredients
Other ingredients consist of pharmaceutical excipients hydrochloric acid (for pH adjustment), sodium chloride and water for injections.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.
No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product containing epirubicin hydrochloride that could be considered a generic medicinal product of Pharmorubicin Solution for Injection 2mg/ml.

The applicant has provided suitable product development information. Valid justification for the use and amount of each excipient has been provided.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches have been provided and are satisfactory.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packaged in type I, clear, colourless, moulded glass vials containing 5 ml, 25 ml, 50 ml and 100 ml of solution. The vials are closed with fluoropolymer coated chlorobutyl rubber stoppers and aluminium polypropylene flip-off seals.

The pack sizes are 1 x 5 ml vial, 1 x 25 ml vial, 1 x 50 ml vial and 1 x 100 ml vial.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with relevant EU legislation.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 18 months for an unopened vial with storage instructions ‘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)’.

The SmPC has the following statement on the shelf-life of the opened product:
‘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.’
‘Epirubicin Solution for Injection does not contain a preservative or bacteriostatic agent. Vials are, therefore for single use only and any unused portion must be discarded after use.’

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPC, PIL and labelling are pharmaceutically acceptable. The SmPC, PIL and labelling that were approved at Day 90 of the procedure by the relevant member states are included in modules 2, 3 and 4 of this report. Subsequent variations to the SmPC, PIL and labelling have been approved since the end of the procedure (please see module 6 at the end of this report for the current approved SmPC, PIL and labelling).

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA form**

The MAA form is pharmaceutically satisfactory.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of epirubicin hydrochloride are well-known. As epirubicin hydrochloride is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

An Environmental Risk Assessment has not been submitted and one is not required for an application of this type.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

Clinical Pharmacology
The applicant’s product is a generic version of the reference product; both products contain the same quantitative and qualitative composition of the drug substance. As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1, no new pharmacokinetic or pharmacodynamic data were submitted with this generic application and none were required. The test and reference products are equivalent solutions at the point of administration; therefore a bioequivalence study is not required for this application.

Efficacy
No new efficacy data were submitted with this application and none were required for an application of this type.

Safety
No new safety data were submitted with this application and none were required for an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA form is clinically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
Given the composition of the product and the intended route of administration, no bioequivalence studies have been performed and none are required for this application.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with epirubicin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
Module 6

**STEPS TAKEN AFTER REPEAT-WAVE MRP PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>27/10/2009</td>
<td>Type II variation</td>
<td>To update sections 1, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4 6.5, 6.6, 7, 8, 9 and 10 of the SPC following the completion of the MRP procedure UK/H/1509/01/MR (10/03/2009).</td>
<td>Approved – 08/01/2010</td>
</tr>
<tr>
<td>19/05/2011</td>
<td>Type II variation</td>
<td>To include additional presentations of 10mg/5ml and 100mg/50ml. SPC sections 2 (Qualitative and quantitative composition) and 6.5 (Nature and contents of container), the PIL and labelling are updated consequentially.</td>
<td>Approved - 18/08/2011</td>
</tr>
<tr>
<td>21/05/2011</td>
<td>Type II variation</td>
<td>To update sections 1 (Name of the medicinal product), 2 (Qualitative and quantitative composition), 4 (Clinical particulars), 5 (Pharmacological properties) and 6 (Pharmaceutical properties) of the SPC, label and leaflet in order to harmonise it with the reference product Pharmorubicin (PL 00032/0275).</td>
<td>Approved – 21/01/2012</td>
</tr>
</tbody>
</table>

Please find attached to the end of this report the current approved SmPC, PIL and Labelling for Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion, which include all changes made from the approved variations listed above, which were submitted subsequent to the end of the Mutual Recognition procedure.
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 50 mg of epirubicin hydrochloride.
Each vial of 50 ml contains 100 mg of epirubicin hydrochloride.
Each vial of 100 ml contains 200 mg of epirubicin hydrochloride.

Excipient (S):
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

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:

<table>
<thead>
<tr>
<th>Cancer indication</th>
<th>Epirubicin Dose (mg/m²)</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>60–90</td>
<td>50</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>50 mg/50 ml or 80 mg/50 ml (carcinoma in situ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prophylaxis: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months</td>
<td></td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>Serum bilirubin</th>
<th>AST (aspartate aminotransferase)</th>
<th>Dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 – 3 mg/100 ml</td>
<td>2 - 4 times the normal upper limit</td>
<td>Dose reduction of 50%</td>
</tr>
<tr>
<td>&gt;3 mg/100 ml</td>
<td>&gt; 4 times the normal limit</td>
<td>Dose reduction of 75%</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Dose Epirubicin required</th>
<th>Volume of 2 mg/ml epirubicin injection</th>
<th>Volume of diluent sterile water for injection or 0.9% sterile saline</th>
<th>Total volume for bladder installation</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg</td>
<td>15 ml</td>
<td>35 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>50 mg</td>
<td>25 ml</td>
<td>25 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>80 mg</td>
<td>40 ml</td>
<td>10 ml</td>
<td>50 ml</td>
</tr>
</tbody>
</table>

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
    - myocardiopathy

  * 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., \( 90 \text{ mg/m}^2 \) 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 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 interaction

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 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 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
The effect of epirubicin on the ability to drive or use machinery has not been systematically evaluated. 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 ≤100); Rare (≥1/10,000 to ≤1/1,000); very rare (≥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.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Common</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Septic shock, sepsis, pneumonia</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Rare</td>
<td>Acute lymphocytic leukaemia, acute myelogenous leukaemia</td>
</tr>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Very Common</td>
<td>Myelosuppression (leucopenia, granucytopenia and neutropenia, anemia and febrile neutropenia)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Haemorrhage and tissue hypoxia as result of myelosuppression.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Anaphylaxis (anaphylactic/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills), allergic reactions following intravesical administration.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Anorexia, dehydration</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hyperuricemia (see section 4.4 )</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Rare</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Peripheral neuropathy (with high doses), headache</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Not known</td>
<td>Conjunctivitis, keratitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
<td>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.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hot flashes</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Phlebitis, thrombophtebitis</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Shock, thromboembolism, including pulmonary emboli</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Mucositis, esophagitis, stomatitis, vomiting, diarrhoea, nausea, which can result in loss of appetite and abdominal pain.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very Common</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Urticaria, pruritis, local erythematous reactions along the vein that was used for the injection.</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Local toxicity, rash, itch, skin changes, erythema,</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Undesirable effects</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>flushes, skin and nail hyperpigmentation, photosensitivity, hypersensitivity to irradiated skin (radiation-recall reaction)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common</td>
<td>Red coloration of urine for 1 to 2 days after administration</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Proteinuria in patients who were treated with a high dose</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Rare</td>
<td>Amenorrhea, azoospermia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Infusion site erythema</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Malaise, asthenia, fever, chills, hyperpyrexia</td>
</tr>
<tr>
<td>Investigations</td>
<td>Rare</td>
<td>Changes in transaminase levels</td>
</tr>
<tr>
<td></td>
<td>Not Known</td>
<td>Asymptomatic drops in left ventricular ejection fraction</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Common</td>
<td>Chemical cystitis, sometimes haemorrhagic, has been observed following intravesical administration (see section 4.4).</td>
</tr>
</tbody>
</table>

**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 leucopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac complications. Latent cardiac failure has been observed with anthracyclines several months to years after completion of treatment (see section 4.4). Patients must be carefully monitored. If signs of cardiac failure occur, patients should be treated according to conventional guidelines.

Treatment:
Symptomatic. Epirubicin cannot be removed by dialysis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic group: 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. The major metabolites that have been identified are epirubicinol (13-OH-epirubicin) and glucuronides of epirubicin and epirubicinol.
The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged drug. Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9% 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 in 72 hours.

The drug does not cross the blood-brain-barrier.

5.3 Preclinical safety data
The main target organs in rat, rabbit and dog following repeated dosing were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the species tested.

It was genotoxic, and, like other anthracyclines, carcinogenic in rats.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
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 Solution for Injection 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

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

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18727/0008
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28 September 2007

10 DATE OF REVISION OF THE TEXT
21/01/2012

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Patient Information Leaflet

PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion

UK/H/1509/001/E01

Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion (Epirubicin hydrochloride)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You need to read it again.
- If you have any doubts or questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

In this leaflet:

1. What this medicine is and what it is used for
2. Before you use epirubicin
3. How to use epirubicin
4. Possible side effects
5. How to store epirubicin
6. Further information

1. WHAT EPIRUBICIN IS AND WHAT IT IS USED FOR

Epirubicin belongs to the therapeutic group of anthracenopic agents (medicine against cancer). It is used either alone or in combination with other anti-cancer medicines.

Epirubicin is used in the treatment of:

- Breast cancer
- Stomach cancer

Epirubicin is also used intravenously to treat early (superficial) uterine bladder cancer and help prevent recurrence of bladder cancer after surgery.

Epirubicin is often used concomitantly with other cancer fighting medicinal products (so-called polychemotherapy schemes).

2. BEFORE YOU USE EPIRUBICIN

Do not use Epirubicin:

- If you are allergic (hypersensitivity) to epirubicin or any of the other ingredients of Epirubicin or to any other similar medicine belonging to a group of medicines called anthracyclines (e.g. doxorubicin and doxorubicin) or anthracyclines.
- If you have had blood cells then normal caused by previous treatment with other antineuronic drugs or by ionizing radiotherapy. Your doctor or pharmacist will advise you.
- If you have been treated with the maximum dose of some other anti-cancer medicines including doxorubicin and doxorubicin which belong to the same group of drugs as epirubicin (called anthracyclines). These medicines have similar side effects (including these effects on the heart).
- If you have suffered or currently have problems with your heart.
- If you have an acute severe infection
- If you have severe liver problems
- If you are breastfeeding.

When administered intravenously directly into the bladder, do not use epirubicin:

- If the cancer has penetrated the bladder wall
- If you have an infection in your urine tract
- If you have pain or inflammation in your bladder
- If there is a large volume of urine left in your bladder after you attempt to empty it
- If you have a cystitis bladder
- If your urine contains blood
- If you have cardiovascular problems.

Take special care with epirubicin:

- to identify the numbers of white and red blood cells and platelets do not drop too low. Your doctor will regularly check this.
- if you are experiencing severe pain or ulcers in your mouth.
- if you have had high tumour protein in your blood. Your doctor will check this.
- if your liver and kidneys are not working properly. This may cause an increase in side effects. Both the kidney function and the liver function will be checked regularly and if needed the dose will be adjusted.
- to ensure your heart is working properly. The dose of epirubicin will have to be adjusted. Your doctor will regularly check this.
- if you have received or are receiving radiotherapy to the chest area or are receiving medications that might have side effects on your heart.
- if you notice a bladder spasm due to or at the injection site during the infusion (possible leakage in the surrounding tissue). Tell your doctor immediately.
- if you desire to have children. Both men and women should use effective contraceptive measures both during and for 6 months after the treatment. Men are advised to seek information about the possibility of storing sperm by means of freezing before the treatment.
- if you are elderly or a child, because of the higher risk of severe cardiac side effects. Your cardiac function will be checked before and after and during the treatment. Epirubicin is not recommended for children.
- if you have previously been treated with products to fight cancer (such as doxorubicin or doxorubicin and anthracyclines) or to have had radiation, because the risk of severe cardiac side effects is greater. Inform your doctor because this is included in determining the total dose of epirubicin you will be administered.
- if you suffer from infections or diarrhoea. Epirubicin may affect the bone marrow. The number of white blood cells in your blood will be reduced, which makes you more susceptible to infections (leucopenia). Breathing problems can occur more easily (respiratory problems). These side effects are temporary in nature. The reduction of the number of white blood cells is greatest 16-14 days after the administration and usually returns to normal 2-3 days after the administration.
- if you have recently received or want to receive any vaccination.
- if you have severe inflammation of the mouth, throat, gagging and gastrointestinal tract.

Please consult your doctor if one of the above mentioned warning is applicable to you, or has been applicable to you in the past.

Taking other medicines:

Please tell your doctor or pharmacist if you have recently taken any other medicines, even those not prescribed, particularly the following:

- Cimetidine (a drug usually used to treat stomach ulcers and heartburn). Cimetidine can make the effects of epirubicin stronger
- other medicines that may affect your heart, for example other medicines against cancer (e.g. cyclophosphamide, cyclopamidine, taxanes), calcium channel blockers (used to control high blood pressure, chest pain, and irregular heartbeat), or concomitant (or prior) radiotherapy to the mediastinal area.
- Quinidine (a drug used for treatment of tachycardia and for arrhythmia)
- Other medicines that may affect the bone marrow: e.g. other cancer treatments, sulphonamides, chlorpyrifos (used to treat infection), diphtheria (used to treat epiglottis, antipyrine-derivate (used to relieve pain), antituberculous agents (used to treat HIV-infection),
- other medicines that may affect your liver: e.g. barbiturates (used to treat epilepsy) or flupenthixol (used to treat hallucinations),
- antipsychotics (used in some cancers),
- interferon-alpha-2b (a drug used in some cancers and lymphomas and for some forms of hepatitis)
- dermaone (a drug sometimes used with doxorubicin to reduce the risk of heart problems)
- the use of epirubicin may be affected by heart conditions
- liver attenuated vaccines

- Prior or concurrent administration of other products related to epirubicin (so-called anthracyclines: for instance the cancer fighting medicine mitomycin-C, dacarbazine, dacarboxym and cyclophosphamide), other medicines that may affect the heart (for instance the cancer fighting medicine 5-fluorouracil, cyclophosphamide, cisplatin, taxanes): the harmlessness to the heart can increase.

- Cyclosporin (a product that suppresses the immune system): the immune system may be suppressed too much.

3. HOW TO USE EPIRUBICIN

Epirubicin will only be given to you under supervision of a doctor specialised in this type of treatment.

Before and during treatment with epirubicin, your doctor will check various laboratory parameters (e.g. blood cell count, blood urea nitrit level, liver function and kidney function) and carefully monitor your heart function. Monitoring of the heart function will be continued for several weeks following the end of treatment with epirubicin.

When given by injection or infusion into a vein

This medicine is given by injection or infusion into a vein.

When given by injection, the usual dose is 60 mg/m2 to 90 mg/m2 body surface area, higher doses (120 mg/m2 to 150 mg/m2 body surface area) may be given by your doctor if you suffer from breast cancer.

Drug is reduced or the following dose may be delayed if you have a low level of white blood cells in your body. If you are elderly, if you have liver problems, or if the drug is used in combination with other antineuronic drugs.

The dose should be prescribed by a professional doctor (e.g. a radiation specialist). The dose will be adjusted according to the type of cancer.

The medicine may be given directly into the bladder using a catheter. If this route is used, you should not drink any fluids for 12 hours before treatment so that your urine will not dilute the drug too much. The urine will therefore remain in the bladder for 2 hours after implantation. You will be instructed occasionally to ensure even exposure of all parts of the bladder to the drug.

Care should be taken to ensure that the contents of the bladder, when emptied, do not come into contact with the skin. In case of skin contact, thoroughly wash the affected area with soap and water but do not rub.

If you received more Epirubicin than you should

If you received more Epirubicin than you should as this medicine will be given to you until you are in hospital it is unlikely that you will be given too much, however, tell your doctor or pharmacist if you have any concerns.

43
PAR Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion

UK/H/1509/001/E01

If you missed a dose of Epirubicin

Epirubicin needs to be given on a fixed schedule. Be sure to keep all appointments. If you miss a dose, you should discuss this with your doctor. Your doctor will decide when you should be given your next dose of epirubicin.

If you stop treatment with Epirubicin

Stopping your treatment with epirubicin may stop the effect on tumour growth. Do not stop treatment with epirubicin unless you have discussed this with your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, aciclovir can cause side effects, although not everybody gets them.

If any of the following happen when epirubicin is given into a vein, tell your doctor immediately:

• any redness, pain or swelling at the injection site. Tissue damage may occur after accidental injection outside the vein.
• symptoms of heart problems such as chest pain, shortness of breath, swelling of your ankles (these effects may occur up to several weeks after finishing treatment with Epirubicin).
• severe allergic reaction, symptoms include: faintness, skin rash, itching, fever, chill, swelling of the face and difficulty in breathing of wheeze. In some cases collapse may occur.
• these are very serious side effects. You may need urgent medical attention.

The following side effects may also occur:

Side effects may appear very common (in more than 1 in 10 patients); uncommon (in more than 1 in 100 but less than 1 in 10 patients); rare (in more than 1 in 1,000 but less than 1 in 100 patients); very rare (less than 1 in 10,000 patients); not known (cannot be estimated from the available data).

Very common:

• restriction of blood cell production in the bone marrow (myelosuppression)
• decreased number of white blood cells (leucopenia)
• neutropenia accompanied by fever (febrile neutropenia)
• decrease in red blood cells (anaemia)
• bleeding (haemorrhages and tissue hypoxia (hypoachae oxygen supply) as a result of myelosuppression)

Common:

• mild reactions: nausea, feeling sick, vomiting, diarrhoea, feeling very dry and thirsty (dehydration), loss of appetite, abdomen pain
• hot flashes
• breast pain
• sensitivity to light or hypersensitivity in the case of radiotherapy
• pain related to a blood clot (thrombophlebitis)
• increased pigmentation (hyperpigmentation) of skin and nails
• skin reddening
• headache

Rare:

• severe hypersensitivity (anaphylaxis) with or without shock including skin rash, pruritus (itching), fever and chill
• ECG changes
• rapid heart rate (tachycardia)
• slow heart rate (bradycardia)
• special forms of arrhythmia (AV block and bundle-branch block)
• third heart sound (gallop rhythm)
• heart muscle disease (cardiomyopathy)
• difficulty in breathing (dyspnoea)
• accumulation of fluid (oedema)
• enlargement of the liver
• accumulation of fluid in the abdominal cavity (ascites)
• lung oedema
• uric acid (uricosuria), with or without shock, redness along the vein that was used for the injection

• absence of menstruation (amenorrhoea)
• lack of sperm in the semen (azoospermia)
• increased levels of liver enzymes (transaminases)
• increased levels of uric acid in the blood (hyperuricaemia) as a result of rapid loss of cancer cells
• malignant tumour of blood-forming tissue (secondary acute myeloid leukaemia), when given in combination with other anti-cancer drugs.

• inflammation of the mucous membrane of the oesophagus (oesophagitis), pigmentation in the mouth.

Side effects unknown:

• fever, infections, inflammation of the lungs (pneumonia), blood poisoning (sepsis) or a state of shock resulting from blood poisoning (septic shock) may occur
• occlusion of blood vessel due to a blood clot (thrombocytopenic events) including occlusion of a blood vessel in the lungs (pulmonary embolism) (in isolated cases with fatal outcome)
• urina turns turbid (proteinuria)
• certain disorders of the nerves (peripheral neuropathy), headache

If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

6. HOW TO STORE EPIRUBICIN

Keep out of the reach and sight of children.

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

Do not use epirubicin after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month. The pharmacist will check this when you need it prepared for you. If the solution is cloudy after preparation, the pharmacist will dispose of it safely.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Epirubicin hydrochloride 2 mg/ml Solution for Injection contains

The active substance is epirubicin hydrochloride. Each ml of solution for injection or infusion contains 2 mg of epirubicin hydrochloride.

The other ingredients are hydrochloric acid, sodium chloride and water for injection.

What Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion looks like and contains the pack

Epirubicin contains 10 mg, 50 mg, 100 mg and 200 mg of the active ingredient, epirubicin hydrochloride, in single glass vials.

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.

Marketing Authorisation Holder and Manufacturer

Pfizer Oncology Plc, Llanbradach, Llantwit Road, Pontyclun, Mid Glamorgan, CF72 8XX, United Kingdom.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria: Epirubicin Kabi 2 mg/ml Injection oder Infusionslösung
Belgium: Epirubicinhydrochloride-Fresenius Kabi 2 mg/ml oplossing voor injectie of infusie
Bulgaria: Еироксихлориди Каби 2 мг/мл индевисионен раствор
Cyprus: Epirubicin Kabi 2 mg/ml Κύπρος ενοεστος ίνεσσης
Czech: Epirubicin Kabi 2 mg/ml
Denmark: Epirubicin Kabi 2 mg/ml
Estonia: Epirubicin Kabi 2 mg/ml
Finland: Epirubicin Kabi 2 mg/ml infektoitorin hallinnos
Germany: Epirubicin Kabi 2 mg/ml Infusionslösung
Greece: Ειροκυκλοριδη Καβι 2 μg/ml ινοεστος ραςστος
Hungary: Epirubicin Kabi 2 mg/ml sódiumtartamónó acidos vágó infúzó
Ireland: Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion
Italy: Epirubicina Kabi 2 mg/ml soluzione iniettabile
Latvia: Epirubicin Kabi 2 mg/ml injekcijas līdzeklis
Lithuania: Epirubicin Kabi 2 mg/ml injekcinis infuzijos priemonė
Luxembourg: Epirubicin Kabi 2 mg/ml Injection oder Infusionslösung
Malta: Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion
Netherlands: Epirubicinhydrochloride-Fresenius Kabi 2 mg/ml oplossing voor injectie of infusie
Norway: Epirubicin Kabi 2 mg/ml injeksjonssøltsett, infusionspakke, oppløsning
Poland: Epirubicin Kabi
Portugal: Epirubicina Kabi
Romania: Epirubicin Kabi 2 mg/ml solutie injectabilă
Slovakia: Epirubicin Kabi 2 mg/ml
Slovenia: Epirubicin Kabi 2 mg/ml reztoplje za injekcijsko infuzijo
Spain: Epirubicin Kabi 2 mg/ml solución inyectable o para perfusión
Sweden: Epirubicin Kabi 2 mg/ml injektions- och infusionslösning
UK: Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion

This leaflet was last approved in January 2012.
The following information is intended for medical and healthcare professional only:

A GUIDE FOR HOSPITAL STAFF

Epirubicin Hydrochloride 2 mg/ml Solution for Injection or Infusion

(Epirubicin hydrochloride)

IMPORTANT: Refer to Summary of Product Characteristics before prescribing.

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.

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).

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.
Labelling

For intravenous or intravesicular use.
For single use only.
Cytotoxic Agent.
Fresenius Kabi Oncology Plc.
POM
PL 18727/0008
PA 1422/2/1

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.

For intravenous or intravesicular use.

Also contains hydrochloric acid, sodium chloride and water for injections.
For single use only.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in a refrigerator (2 °C to 8 °C). Do not freeze. Keep vial in the outer carton in order to protect from light.
Cytotoxic Agent. Discard any unused solution.
For appropriate disposal, refer the package leaflet.
Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion

50 mg/25 ml

For intravenous or intravesicular use

Each ml of solution for injection or infusion contains 2 mg of epirubicin hydrochloride.
Each vial of 25 ml contains 50 mg of epirubicin hydrochloride.

Also contains hydrochloric acid, sodium chloride and water for injections.

For single use only.
For intravenous or intravesicular use.

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

Cytotoxic Agent. Discard any unused solution.

For appropriate disposal, refer the package leaflet.

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

PL 18727/0008
PA 1422/2/1

Batch No:
Exp:

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Epirubicin hydrochloride 2 mg/ml Solution for Injection or Infusion

Each ml of solution for injection or infusion contains 2 mg of epirubicin hydrochloride.
Each vial of 100 ml contains 200 mg of epirubicin hydrochloride.

Also contains hydrochloric acid, sodium chloride and water for injections.

For single use only.

Keep out of the reach and sight of children.

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

Cytotoxic Agent. Discard any unused solution.

For appropriate disposal, refer the package leaflet.

1 x 100 ml Vial

Fresenius Kabi Oncology Plc.
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