Safeguarding public health

MHRA

Public Assessment Report

Epirubicin 2mg/ml Solution for Injection

PL 19364/0015

Applicant: UKR Regulatory Affairs Limited

Medicines and Healthcare products Regulatory Agency

Epirubicin 2mg/ml Solution for Injection
PL 19364/0015

LAY SUMMARY

The MHRA has granted UKR Regulatory Affairs Limited a Marketing Authorisation (licence) for the medicinal product Epirubicin 2mg/ml Solution for Injection (PL 19364/0015). Epirubicin 2mg/ml Solution for Injection is a prescription-only medicine (POM) that contains epirubicin and is used to treat a variety of cancers, either alone or in combination with other drugs. The way in which it is used depends upon the type of cancer that is being treated.

Epirubicin belongs to a group of drugs called anthracycline antibiotics, drugs that slow or stop the growth of actively growing cells (such as cancer cells). When injected into the bloodstream, Epirubicin has been found to be useful in the treatment of cancers of the breast, ovaries, stomach, bowel and lung. Epirubicin can be given the same way to treat cancers in the bone marrow such as malignant lymphomas, leukaemias and multiple myeloma.

Epirubicin 2mg/ml Solution for Injection can also be passed into the bladder through a tube that is inserted through the urethra, (the tube through which urine flows). It may be given this way to treat abnormal cells or cancers in the bladder wall. It can also be used after other treatments to try and prevent such cells from growing again.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Epirubicin 2mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been approved.

Epirubicin 2mg/ml Solution for Injection
PL 19364/0015

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusions and risk benefit assessment	Page 10

INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Epirubicin 2mg/ml Solution for Injection (PL 19364/0015) to UKR Regulatory Affairs Limited on 26th October 2007. The product is available as a prescription-only medicine (POM).

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, as a generic medicinal product of the original product Pharmorubicin Injection 2mg/ml (Farmitalia Carlo Erba Limited) which has been authorised in the EU for more than 10 years.

The product contains the active ingredient epirubicin hydrochloride and is indicated for a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma. Also, intravesical administration of epirubicin hydrochloride has been found to be beneficial in the treatment of superficial bladder cancer, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

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 SAl8O (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).

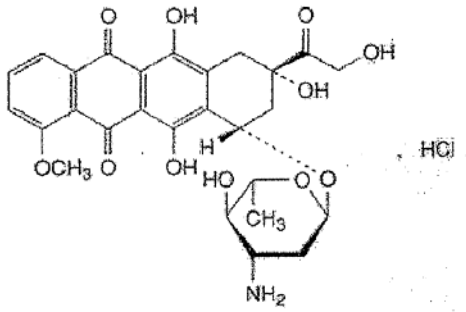
PHARMACEUTICAL ASSESSMENT

Active substance

INN: Epirubicin hydrochloride

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

Structure:



Molecular Formula: $C_{27}H_{29}NO_{11}$, HCl

Molecular Weight: 579.99

Epirubicin hydrochloride is an orange-red crystalline powder and practically odourless. It has a melting point of 185ºC. It has an optical rotation in 1% methanol of +274. It is soluble in water and in methanol, slightly soluble in ethanol and practically insoluble in acetone.

Epirubicin hydrochloride is the subject of a European pharmacopoeial monograph.

The manufacture and control of the active substance epirubicin hydrochloride is covered by a European Pharmacopoeia Certificate of Suitability. A statement has been provided that no materials of animal or human origin have been used in the manufacture of active epirubicin hydrochloride.

A suitable active substance specification has been provided that is in-line with the certificate of suitability. Batch analysis data have been provided which are consistent with the proposed specification.

The active epirubicin hydrochloride is stored in low-density polyethylene bags, which are placed in aluminium-coated bags and packed in aluminium tins. Appropriate stability data have been generated to support a retest period of 24 months when stored in the proposed packaging.

Other ingredients

Other ingredients consist of water for injections, sodium chloride and hydrochloric acid. Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective European Pharmacopoeia monograph.

None of the excipients are sourced from materials of animal or human origin.

The commercial packaging consists of a Type I borosilicate glass vials, with a film-coated chlorobutyl stoppers and aluminium seals. Vial sizes are 15ml (for 10mg/5ml and 20mg/10ml

pack sizes), 50ml (for 50mg/25ml and 100mg/50ml pack sizes) and 100ml (for 200mg/100ml pack size). The vials are packed into cartons in pack sizes of 1, 6, 10, 12, 20, 50 and 100 vials.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. The glass vials and film-coated rubber stoppers have been shown to comply with current guidelines concerning the use of materials in contact with injectable products. All components of the container-closure system are sterilised before use to make them suitable for the asceptic production of the finished product.

Product development, manufacture and finished product specification
The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

A comparison of the impurity profiles, pH and epirubicin content between the proposed product and several European comparators has been performed. The results confirmed that the proposed product can be considered as a generic medicinal product to Pharmorubicin Injection 2mg/ml.

Satisfactory batch formulae have 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.

The finished product specifications proposed is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. All impurities expected in the final product have been characterised. Batch analysis data has demonstrated compliance with the proposed release specifications. Acceptable certificates of analysis have been provided for all reference standards used.

Stability of the product
Stability data have been provided, in compliance with ICH guidelines, for solution produced by the finished product manufacturer in all packaging proposed for marketing. These data support a shelf-life of 2 years, with storage conditions ‘Keep container in the outer carton’, and ‘Store in refrigerator (2-8°C)’. An additional shelf-life limit of 24 hours is stated after opening or reconstitution of the product.

The applicant has committed to continuing the ongoing stability studies in accordance with the submitted stability protocol.

Bioequivalence/bioavailability
As this is a product for injection, no bioequivalence data are provided and none are required.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar impurity, pH and assay profiles have been provided for the proposed and reference products.

PRECLINICAL ASSESSMENT

This application is a generic product of Pharmorubicin Injection 2mg/ml (Farmitalia Carlo Erba Limited), which have been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

The indications are consistent with those for the reference product and are satisfactory.

2. DOSE & DOSE SCHEDULE

The dose and dosage schedule are consistent with those for the reference product and are satisfactory.

3. CLINICAL PHARMACOLOGY

The clinical (and preclinical) expert reports provide an adequate review of the known pharmacodynamics and pharmacokinetics of epirubicin hydrochloride. No reference is made to any new data that would have affected the product under consideration.

No bioequivalence data have been submitted or are required for this product.

4. EFFICACY

The clinical expert report provides an adequate review of the efficacy of epirubicin hydrochloride for the listed indications.

5. SAFETY

The clinical expert report provides an adequate review of the clinical safety of epirubicin hydrochloride. The toxicity from epirubicin hydrochloride is described in detail per organ system. No reference is made to any new data that would have affected the marketing authorisation for the product under consideration.

6. EXPERT REPORTS

The clinical expert report is written by an appropriately qualified medic.

7. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is consistent with the reference product and is satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)

This is consistent with the reference product and is satisfactory.

9. LABELLING

Full colour mock-ups are provided and are satisfactory.

10. MEDICAL CONCLUSION

A marketing authorisation may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Epirubicin 2mg/ml Solution for Injection 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

As the product is a simple aqueous solution for injection, containing identical excipients to that of the brand leader, no bioequivalence data were required and the proposed product is considered to be a generic medicinal product of the brand leader. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical 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 risk benefit is, therefore, considered to be positive.

Epirubicin 2mg/ml Solution for Injection
PL 19364/0015

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23rd February 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 13th March 2006
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 19th July 2006 and 14th September 2006, and quality dossiers on 17th July 2006 and 1st August 2007
4	The applicant responded to the MHRA's requests, providing further information for the clinical dossier on 14th September 2006 and 27th March 2007 and quality dossier on 11th November 2006 and 12th September 2007
5	The applications were determined on 24th October 2007

Epirubicin 2mg/ml Solution for Injection
PL 19364/0015

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2 mg/ml Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains 10 mg epirubicin hydrochloride.
Each 10 ml vial contains 20 mg epirubicin hydrochloride.
Each 25 ml vial contains 50 mg epirubicin hydrochloride.
Each 50 ml vial contains 100 mg epirubicin hydrochloride
Each 100 ml vial contains 200 mg epirubicin hydrochloride.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Dark red clear solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epirubicin has produced responses in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma.

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

4.2 Posology and method of administration

Intravenous administration: Epirubicin is not active when given orally and should not be injected intramuscularly or intrathecally.

It is advisable to give the drug via the tubing of a freely running IV saline infusion after checking that the needle is well placed in the vein (see section 6.6). 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. 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 60-90 mg/m^2 body area; the drug should be injected IV over 3-5 minutes and, depending on the patients' haematomedullary status, the dose should be repeated at 21 day intervals.

Safety and efficacy in children have not been established.

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

Lung cancer
Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.

Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day 1 or 45 mg/m^2 days 1, 2, 3, every 3 weeks.

Breast cancer
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3-4 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 3-5 minutes or as an infusion up to 30 minutes. Lower doses (60-75 mg/m^2 for conventional treatment and 105-120 mg/m^2 for high dose schedules) are recommended for patients whose bone marrow function has already been impaired by previous

chemotherapy or radiotherapy, by age, or neoplastic bone-marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

When the drug is used in combination with other antitumour agents, the doses need to be adequately reduced. Since the major route of elimination of Epirubicin is the hepatobiliary system, the dosage should be reduced in patients with impaired liver function, in order to avoid an increase of overall toxicity. Moderate liver impairment (bilirubin: 1.4-3 mg/100ml) requires a 50% reduction of dose, while severe impairment (bilirubin> 3 mg/100 ml) necessitates a dose reduction of 75%.

Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of Epirubicin excreted by this route.

Intravesical administration:
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.

While many regimens have been used, the following may be helpful as a guide: for therapy 8 x weekly instillations of 50 mg/50 ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50 ml is advised. For carcinoma-in-situ, depending on the individual tolerability of the patient, the dose may be increased up to 80 mg/50 ml. For prophylaxis, 4 x weekly administrations of 50 mg/50 ml followed by 11 x monthly instillations at the same dosage, is the schedule most commonly used

The solution should be retained intravesically for 1 hour. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 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 (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Epirubicin is contraindicated in patients with marked myelosuppression induced by previous treatment with other antitumour agents or by radiotherapy and in patients already treated with maximal cumulative doses of other anthracyclines such as Doxorubicin or Daunorubicin.

The drug is contraindicated in patients with current or previous history of cardiac impairment.

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. Treatment with high dose Epirubicin in particular requires the availability of facilities for the care of possible clinical complications due to myelosuppression.

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

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

Before starting therapy and if possible during treatment, liver function should be evaluated (SGOT, SGPT, alkaline phosphatase, bilirubin). A cumulative dose of 900-1000 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses.

Above this level the risk of irreversible congestive cardiac failure increases greatly. There is objective evidence that the cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of cardiac failure of the type described for other anthracyclines.

Heart failure can appear even several weeks after discontinuing treatment, and may prove 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.

In establishing the maximal cumulative doses of Epirubicin, any concomitant therapy with potentially cardiotoxic drugs should be taken into account.

It is recommended that an ECG before and after each treatment cycle should be carried out. 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.

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 ejection fraction. 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, echocardiography and, if necessary, measurement of ejection fraction by radionuclide angiography.

Like other cytotoxic agents, Epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be carefully checked so that this phenomenon may be controlled pharmacologically.

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

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin be mixed with other drugs. But Epirubicin can be used in combination with other anticancer drugs.

Cimetidine increases the formation of the active metabolite of epirubicin and the exposure of the unchanged epirubicin by pharmacokinetic interaction.

4.6 Pregnancy and lactation

There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals.

4.7 Effects on ability to drive and use machines

Epirubicin 2 mg/ml Injection has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Blood and lymphatic system disorders: Myelosuppression.

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with epirubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 year) latency period.

High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have 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 a few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Cardiac disorders: Cardiotoxicity.

Gastrointestinal disorders: Mucositis may appear 5-10 days after the start of treatment, and usually involves stomatitis with areas of painful erosions, mainly along the side of the tongue and the sublingual mucosa.

Nausea, vomiting and diarrhoea.

Skin and subcutaneous tissue disorders: Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.

Renal and urinary disorders: During intravesical administration, as drug absorption is minimal, systemic side effects are rare; more frequently chemical cystitis, sometimes haemorrhagic, has been observed.

General disorders: Hyperpyrexia.

Fever, chills and urticaria have been rarely reported; anaphylaxis may occur.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anthracyclines and related substances,

ATC code L01DB

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 60-150mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. 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 9-10% 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

Sodium chloride
Hydrochloric acid
Water for Injections

6.2 Incompatibilities

Prolonged contact with any solution 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

2 years

After first opening:
Chemical and physical in-use stability has been demonstrated for 24 hours at 5°C.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution
Chemical and physical in-use stability have been demonstrated after dilution in 0.9% sodium chloride solution or 5% Dextrose solution for 24 hours at 25^{o}C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C)
Keep the vials in the outer carton

6.5 Nature and contents of container

Clear Type I glass vials (containing 5 ml, 10 ml, 25 ml, 50 ml or 100 ml) with chlorobutyl stoppers and aluminium seals with flip off tops.

Packs of 1, 6, 10, 12, 20, 50 or 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

Intravesical administration. Epirubicin should be instilled using a catheter and retained intravesically for 1 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.

7 MARKETING AUTHORISATION HOLDER

UKR Regulatory Affairs Ltd
Chiltern House
Thame Road
Haddenham
Bucks
HP17 8BY

8 MARKETING AUTHORISATION NUMBER(S)

PL 19364/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2007

10 DATE OF REVISION OF THE TEXT

26/10/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Epirubicin 2 mg/ml Solution for Injection

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your 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 please tell your doctor or pharmacist.

In this leaflet:

1. What Epirubicin 2 mg/ml Solution for Injection is and what it is used for
2. Before you use Epirubicin 2 mg/ml Solution for Injection
3. How to use Epirubicin 2 mg/ml Solution for Injection
4. Possible side effects
5. How to store Epirubicin 2 mg/ml Solution for Injection
6. Further information

1. What Epirubicin 2 mg/ml Solution for Injection is and what it is used for

Epirubicin belongs to a group of medicines called anthracycline antibiotics (a drug that slows or stops the growth of actively growing cells such as cancer cells).

Epirubicin is used in the treatment of breast, ovarian, stomach, lung and bowel cancer. It is also used in the treatment of malignant lymphoma such as Hodgkin's disease and non-Hodgkin's lymphoma, leukaemia, multiple myeloma and non-invasive bladder cancer. Epirubicin may also be used to help prevent recurrence of bladder cancer after surgery.

2. Before you use Epirubicin 2 mg/ml Solution for Injection

Do not use Epirubicin 2 mg/ml Solution for Injection if:
- You ever had an allergic reaction to epirubicin or to any of the other ingredients listed below (section 6)
- You have fewer blood cells than normal (your doctor will check this)
- You have already been treated with the maximum dose of epirubicin or other anthracycline drugs such as doxorubicin and daunorubicin
- You have, or have had previously, heart problems
- You are pregnant or breast-feeding

Take special care with Epirubicin 2 mg/ml Solution for Injection if:
- You have liver disease
- You have received or are receiving radiotherapy to the chest area
- You are taking any drugs which affect your heart function

Your doctor will do regular tests to ensure that the number of your blood cells does not fall too low, to ensure that your heart is working properly and to check the level of uric acid in your blood.

Epirubicin should be given to you by an individual experienced in the use of chemotherapy drugs.

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. Especially:

- Cimetidine (a drug used to reduce the acid in your stomach)

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding do not take this medicine until you have talked to your doctor. Consult your doctor immediately if you or your partner becomes pregnant whilst you are taking this medicine.

Important information about some of the ingredients of Epirubicin 2 mg/ml Solution for Injection
This medicinal product contains 3.5mg sodium in every millilitre of solution.

3. How to use Epirubicin 2 mg/ml Solution for Injection

Your medicine comes in the form of a solution for injection.

- Your doctor will decide the correct dose to use depending on the type of cancer that you have, your health and if you have liver problems. The dose is worked out by the patient's height and weight which gives their body surface area.

- Epirubicin will be given by a doctor or nurse directly into a vein over 3-5 minutes (intravenously), or in a drip by infusion into a vein over 30 minutes.
  The treatment can be repeated at 3 week intervals if necessary.

- Epirubicin may also be given directly into the bladder to treat bladder cancer or to help prevent it returning. If you are to be treated in this way you should not drink any fluids for 12 hours before treatment so that your urine does not dilute the medicine.

The solution will be kept in your bladder for 1 hour, during which time you will be rotated occasionally so that the medicine comes into contact with all parts of your bladder.

Your doctor will decide on the number of courses of treatment that you require.

Combination therapy:
If you are taking other medicines at the same time as epirubicin, your doctor will adjust your dose as necessary.

If you use more Epirubicin 2 mg/ml Solution for Injection than you should
This medicine will usually be given to you by a healthcare professional, if you think that you may have missed a dose or have received too much medicine please tell your doctor or nurse **immediately**.

4. Possible side effects

Like all medicines, Epirubicin 2 mg/ml Solution for Injection can cause side effects in some patients, although not everybody gets them.

Some people may find they have an allergic reaction to epirubicin. Tell your doctor immediately if any of the following rare severe allergy symptoms occur:
- **Sudden wheeziness and tightness of the chest**
- **Swelling of eyelids, face or lips**
- **Skin rashes or lumps, itchiness, fever**
- **Collapse**

You should also tell your doctor immediately if you feel pain or a burning or stinging sensation at the place where the medicine goes into your vein.

You may notice the following side effects in between courses of treatment:
- If you get a fever, chills or rashes it is important to tell your doctor immediately as you may be allergic to epirubicin solution.
- Your doctor should test your blood cell levels to make sure they are not too low.
- Low red blood cell levels (anaemia) can leave you feeling tired and lethargic.
- Low white blood cell levels can increase the chance of infections and raised temperature or fever.
- Blood platelets (help blood clotting) can be affected as well causing you to bruise easily and bleed more than usual if you cut yourself. If this happens seek medical advice.
- Appearance of urine is red in colour for 1-2 days after taking the medicine, this is related to the colour of the medicine.
- Hair loss is common and beard growth in men may stop. The hair normally grows back when the treatment is stopped.
- Mouth ulcers and inflammation of the mouth may occur, and there maybe a feeling of sickness (nausea), vomiting (being sick) and diarrhoea.

Epirubicin when given in combination with other anti-cancer drugs can cause secondary leukaemia after completing treatment. This is rare.

Epirubicin used in the urinary bladder may cause cystitis (inflammation of the urinary bladder).This has been known to be painful and sometimes cause bleeding into the urine. A burning sensation may be felt due to the inflammation when you pass urine. If this happens let your doctor know.

Your doctor will check your blood levels for low blood cell counts that may need treatment, and to check that epirubicin is not affecting your liver function in a harmful way.

Your heart function will also be monitored by your doctor as epirubicin can have effects on this.

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

5. How to store Epirubicin 2 mg/ml Solution for Injection

Keep out of the reach and sight of children

Epirubicin 2mg/ml Solution for Injection should be properly stored before it is administered to you.

The unopened vial should be kept in the outer carton in order to protect from light and stored at 2-8°C (in a refrigerator).

Do not use Epirubicin 2 mg/ml Solution for Injection after the expiry date printed on the label or carton.

6. Further information

What Epirubicin 2 mg/ml Solution for Injection contains
This medicinal product comes in five different vial sizes:
Epirubicin 10 mg/5 ml Solution for Injection contains 10 mg epirubicin hydrochloride which is the active ingredient.
Epirubicin 20 mg/10 ml Solution for Injection contains 20 mg epirubicin hydrochloride which is the active ingredient.
Epirubicin 50 mg/25 ml Solution for Injection contains 50 mg epirubicin hydrochloride which is the active ingredient.
Epirubicin 100 mg/50 ml Solution for Injection contains 100 mg epirubicin hydrochloride which is the active ingredient.
Epirubicin 200 mg/100 ml Solution for Injection contains 200 mg epirubicin hydrochloride which is the active ingredient.

The other ingredients are:
- Water for Injection.
- Sodium chloride.
- Hydrochloric acid

The following vial sizes are available:
5 ml, 10 ml, 25 ml, 50 ml and 100 ml vials in packs of 1, 6, 10, 12, 20, 50 or 100 vials.*
*Not all pack sizes may be marketed.

What Epirubicin 2 mg/ml Solution for Injection looks like and the contents of the pack
Your medicinal product comes in a clear glass vial with a rubber stopper and aluminium cap which is packed into a carton along with this patient information leaflet.
The vial contains a solution for injection which is a dark red, clear solution.

Marketing authorisation holder and manufacturer

Marketing Authorisation Holder:
UKR Regulatory Affairs Ltd, Chiltern House, Thame Road, Haddenham, Bucks, HP17 8BY.

Manufacturer:
Genepharm S.A, 18th km Marathonos Av., 153 51 Pallini Attikis, Greece.
Merckle GmbH, Ludwig-Merckle-Strasse 3, D-89143 Blaubeuren, Germany.

This leaflet was last approved in

Technical Leaflet – Information for the healthcare professional

Incompatibilities

Prolonged contact with any solution 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.

Special precautions for storage

This medicine should be stored at 2-8°C (in a refrigerator).
Keep the glass vial in the outer carton in order to protect from light.
Chemical and physical in-use stability has been demonstrated for 24 hours at 5°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.
Do not use Epirubicin 2 mg/ml Solution for Injection after the expiry date printed on the label or carton.
Chemical and physical in-use stability has been demonstrated after dilution in 0.9% sodium chloride solution and 5% dextrose solution for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Nature and contents of container

Cardboard carton containing a colourless Type I glass vial with a chlorobutyl rubber stopper and aluminium seal with flip off top.

5 ml, 10 ml, 25 ml, 50 ml or 100 ml vials containing Epirubicin 2mg/ml.

Instructions for use and handling

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

EPIRUBICIN
2 mg/ml
SOLUTION FOR INJECTION
10 mg/5 ml

Solution for Injection or Infusion
For intravenous use
Read the package leaflet before use

Each 5 ml vial contains 10 mg epirubicin hydrochloride.
Also contains: Sodium chloride, hydrochloric acid and Water for Injections.

Keep out of the reach and sight of children.
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.

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EPIRUBICIN
2 mg/ml
SOLUTION FOR INJECTION
20 mg/10 ml

Solution for Injection or Infusion
For intravenous use
Read the package leaflet before use

Each 10 ml vial contains 20 mg epirubicin hydrochloride.
Also contains: Sodium chloride, hydrochloric acid and Water for Injections.

Keep out of the reach and sight of children.
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.

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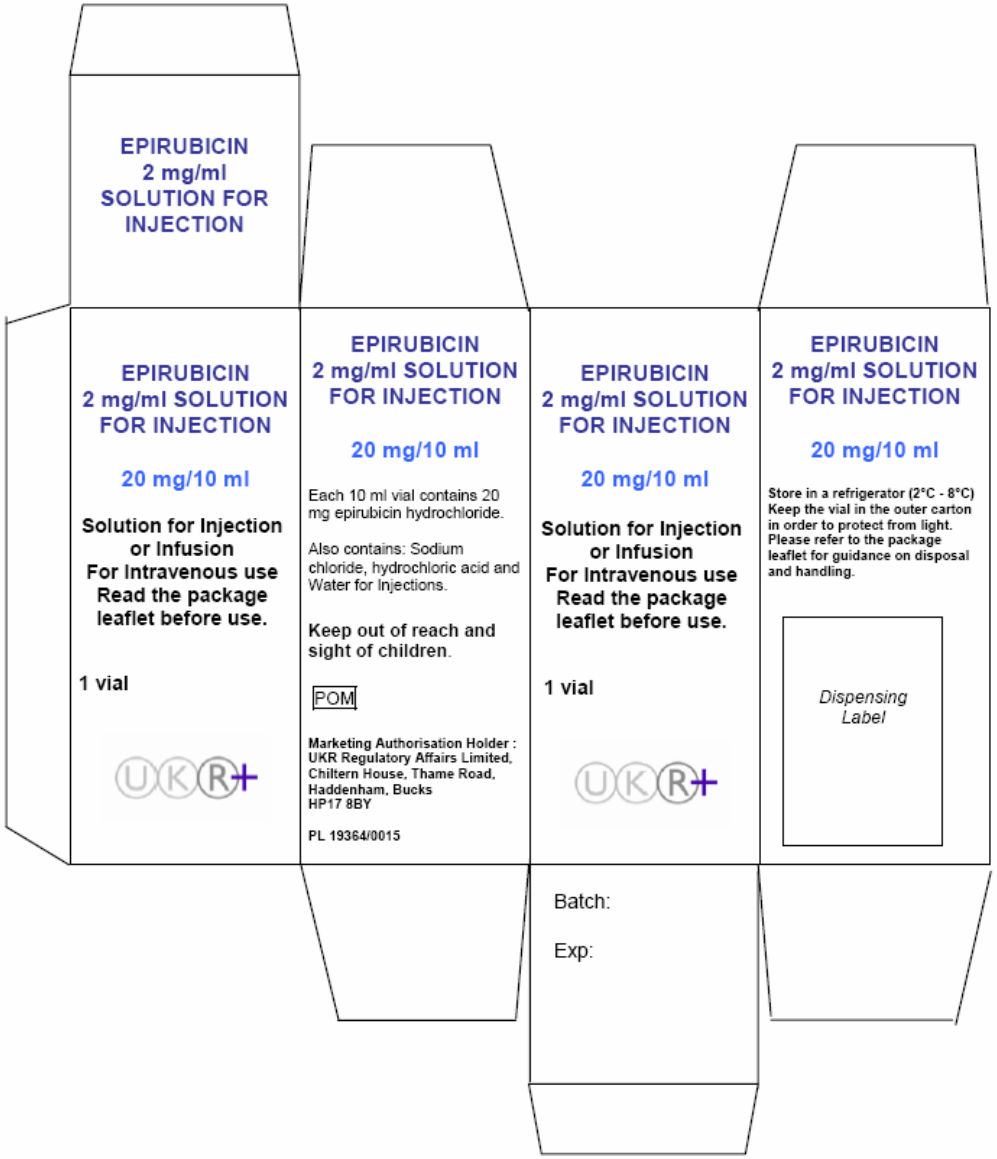

EPIRUBICIN
2 mg/ml
SOLUTION FOR INJECTION

50 mg/25 ml

Solution for Injection or Infusion
For intravenous use
Read the package leaflet before use

Each 25 ml vial contains 50 mg epirubicin hydrochloride.
Also contains: Sodium chloride, hydrochloric acid and Water for Injections.

Keep out of the reach and sight of children.
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.

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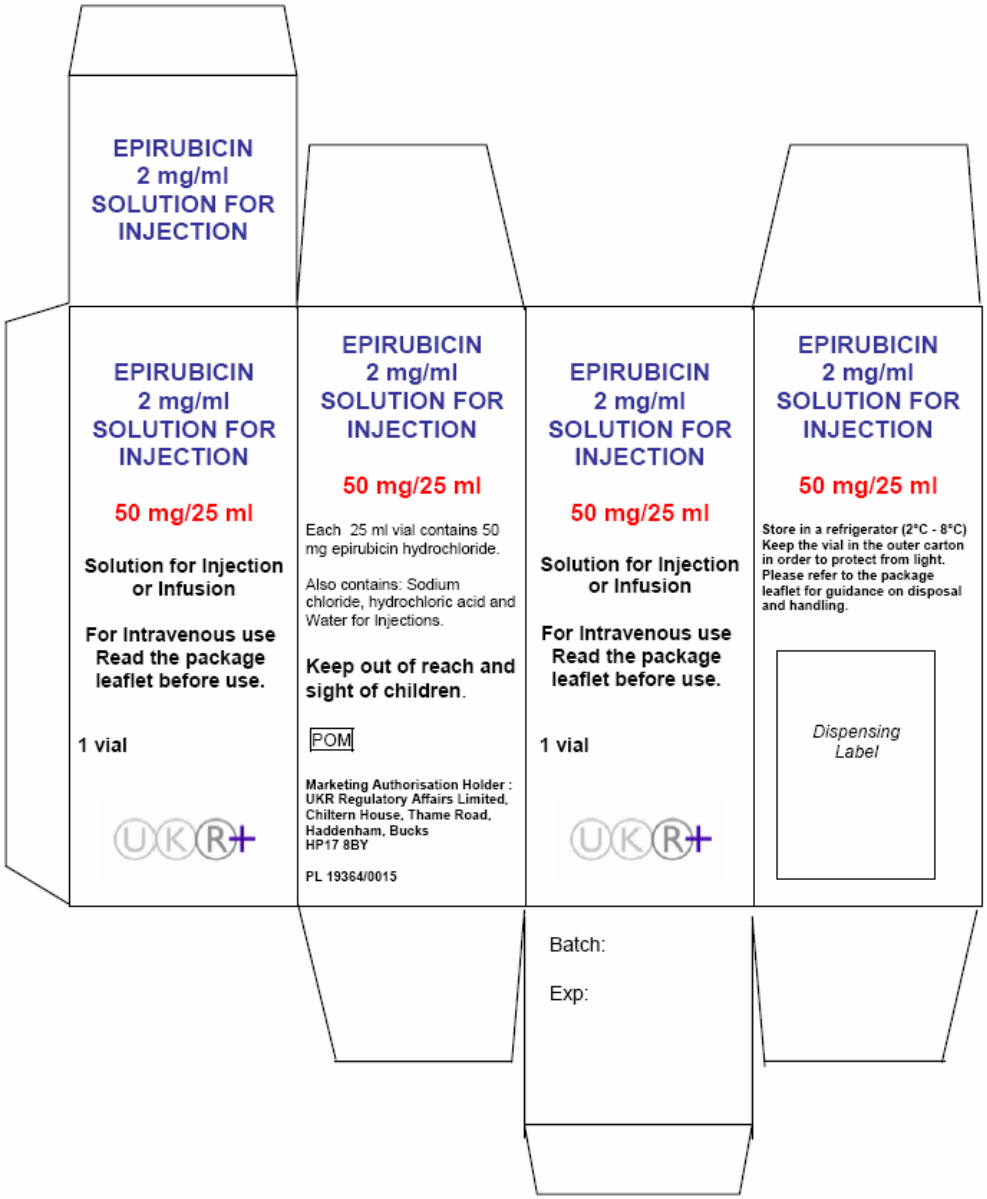

EPIRUBICIN
2 mg/ml
SOLUTION FOR INJECTION

100 mg/50 ml

Solution for Injection or Infusion
For intravenous use
Read the package leaflet before use

Each 50 ml vial contains 100 mg epirubicin hydrochloride.
Also contains: Sodium chloride, hydrochloric acid and Water for Injections.

Keep out of the reach and sight of children.
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.

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EPIRUBICIN
2 mg/ml
SOLUTION FOR INJECTION

200 mg/100 ml

Solution for Injection or Infusion
For intravenous use
Read the package leaflet before use

Each 100 ml vial contains 200 mg epirubicin hydrochloride.
Also contains: Sodium chloride, hydrochloric acid and Water for Injections.

Keep out of the reach and sight of children.
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.

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UKR Regulatory Affairs Ltd.
Chiltern House, Thame Road
Haddenham, Bucks.
HP 17 8BY, UK

Batch:
Exp: