EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION (10MG IN 5 ML)

PL 04543/0491

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION (50MG IN 25ML)

PL 04543/0492

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION (100MG IN 50ML)

PL 04543/0493

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION (200MG IN 100ML)

PL 04543/0494

UKPAR

TABLE OF CONTENTS

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0491-4

LAY SUMMARY

The MHRA granted CP Pharmaceuticals Limited Marketing Authorisations (licences) on the 23rd February 2006, for Epirubicin 2mg/ml, concentrate for solution for injection or infusion, 10mg in 5ml, 50mg in 25ml, 100mg in 50ml and 200mg in 100ml. These Prescription Only Medicines (POM) are used to treat a wide range of neoplastic conditions.

Epirubicin 2mg/ml concentrate for solution for injection or infusion contains the active ingredient epirubicin hydrochloride, which is an anthracycline cytotoxic agent.

The clinical data presented to the MHRA, pre licensing, demonstrated that Epirubicin 2mg/ml concentrate for solution for injection or infusion is essentially similar or equivalent to the approved product, Pharmorubicin 2mg/ml concentrate for solution for injection or infusion (PL 00032/0275) and, as such, can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Epirubicin 2mg/ml concentrate for solution for injection or infusion outweigh the risks, hence Marketing Authorisations have been granted.

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0491-4

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for Epirubicin 2mg/ml concentrate for solution for injection or infusion (10mg in 5ml, 50mg in 25ml, 100mg in 50ml and 200mg in 100ml) to CP Pharmaceuticals Limited on 23rd February 2006. The product is a Prescription Only Medicine (POM)

The applications were submitted as abridged applications according to article 10.1(a) (iii) of Directive 2001/83/EC as amended, claiming essential similarity to the approved product, Pharmorubicin solution for injection 2mg/ml (PL 00032/0275) which, itself, cross-referred to Pharmorubicin Injection 2 mg/ml (PL 03433/0135).

The product contains the active ingredient epirubicin hydrochloride and is indicated in the treatment of a range of neoplastic conditions including breast, ovarian, gastric, lung and colorectal carcinomas, malignant lymphomas, leukaemias and multiple myeloma. When administered intravesically, epirubicin has been shown to be beneficial in the treatment of papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and 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

1. INTRODUCTION

These are abridged applications for Marketing Authorisation in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

The original product is listed as Pharmorubicin 2mg/ml licensed in the UK on the 18th January 1991 to Farmitalia Carlo Erba Ltd (PL 03433/0135).

Though PL 03433/0135 was an existing licence when this application was submitted, it has since been cancelled (14th November 2004). The current UK product is PL 00032/0275 granted to Pharmacia on the 14th May 2004.

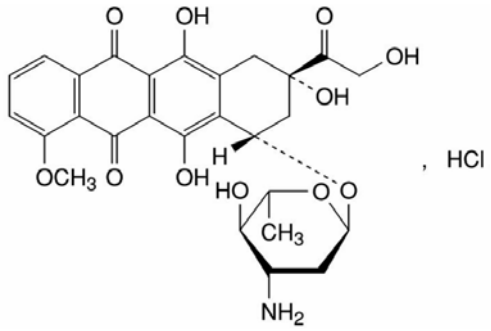
2. DRUG SUBSTANCE

2.1 General information

Current Certificates of Suitability have been supplied by the drug substance manufacturers. There is no re-test date on the certificates of suitability.

Acceptable certification on the TSE status has been supplied.

Structure:



Description: Red orange powder

Chemical name: 5,12-Naphthacenedione,10-[(3-amino-2,3,6-trideoxy-a-Larabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride, (8S-cis)-

Molecular formula: $C_{27}H_{30}ClNO_{11}$

Relative molecular mass: 579.99

Chirality:	The substance has 6 stereogenic centres, the same as in daunorubicin, doxorubicin and other daunorubicin analogues. It differs from doxorubicin only in the position of the C4 hydroxyl group of the sugar moiety.
Polymorphs:	Epirubicin hydrochloride is obtained by lyophilization of a highly purified solution, so that an amorphous modification is obtained.

2.2 Manufacture

2.2.1 Manufacturing process

Both manufacturers are stated as using the same synthetic route.

2.2.2 Impurities

In addition to the impurities listed in the European Pharmacopoeia, the EDQM requested that the following be added to the transparency list as 'other detectable impurities', N-trifluorouracetyl daunorubicin, 4'carbonyl-N-trifluoroacetyl daunorubicin, 4'-epi-14-bromodaunorubicin and daunorubicinol.

2.3 Control of active substance

2.3.1 Specification

The specification for epirubicin hydrochloride has been supplied by the finished product manufacturer . This includes the requirements of the European Pharmacopoeia. The control of the active substance from the two active ingredient manufacturers has been harmonised by the finished product manufacturer.

The specification covers the additional testing stated on the Certificates of Suitability.

2.3.2 Analytical test methods

Relevant details have been provided for the pharmacopoeia methods used by the finished product manufacturer.

No validation data has been presented for the pharmacopoeia methods. Validation data has been provided for the related substances and content in the finished product section as the same methods have been used.

2.3.3 Batch analyses

Assessment of batches by the finished product manufacturer demonstrates compliance to the specifications and inter-batch conformity.

2.3.4 Reference standards

Relevant information on the reference standards has been supplied.

2.3.5 Container closure system

The certificate of suitability has been referenced.

2.3.6 Stability

Stability data has been provided by both active ingredient manufacturers for batches of varying sizes, stored at long-term, intermediate and accelerated conditions.

On the basis of all the data provided a re-test period of 24 months has been stated at 2°C-8°C. A post approval stability commitment has been provided to complete the studies.

It has been confirmed that the post approval stability commitment of both active ingredient manufacturers will include one commercial batch per year stored at the proposed storage conditions.

3. DRUG PRODUCT

3.1 Composition

The qualitative composition of the products are summarised in table 1. The products are solutions for injection and infusion. The products are concentrates at a concentration of 2mg/ml.
The products are packed in colourless type I glass vials with a filling capacity of 5ml, 50ml (for both 50mg/25ml and 100mg/50ml products) and 100ml. The vials have a fluoropolymer-coated chlorobutyl rubber stopper with a metal cap.

Table 1

Ingredients	Function	Quality reference
Epirubicin hydrochloride	Active	Ph. Eur.
Sodium chloride	Isotonic agent	Ph. Eur.
Hydrochloric acid dilute	pH adjustment	Ph. Eur.
Water for injections	Solvent	Ph. Eur.

The amount of hydrochloric acid depends on the quantity necessary for pH adjustment with a corresponding adjustment in the water.

3.2 Pharmaceutical Development

3.2.1 Formulation development

Epirubicin hydrochloride is soluble in water consequently an aqueous solution has been used with sodium chloride used as an isotonic agent, which is a reasonable approach.

The solution is used at a concentration of 2mg/ml, lower concentrations result in an unnecessarily large volume, whereas high concentrations might precipitate at the storage temperature of 2°C to 8°C. This is also the concentration of the reference product.

Compatibility of epirubicin hydrochloride and the excipients has been assumed indirectly from the stability results.

3.2.3 Manufacturing development

The manufacturing process for the incorporation of the ingredients would be considered to be fairly straight forward, due to the reasonable solubility.

3.2.4 Container closure system

Amber and colourless glass vials demonstrated no significant differences under accelerated conditions. Colourless glass vials were selected to ensure easy optical control.

3.3 Manufacture

3.3.1 Manufacturer(s)

A GMP certificate has been supplied for the manufacturing site from the relevant authorities.

3.3.2 Batch formula

The batch formula for four different batch sizes has been presented. The same equipment is used for all filtration, filling and control operations.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A written summary of the process has not been included.

The run time is stated as being not more than 24 hours from preparing the materials to sealing the vials.

3.3.4 Reprocessing

No reprocessing is performed.

3.3.5 Control of critical steps (in-process controls)

Brief details of the methods used have been provided. The in-process controls are suitable and specifications have been provided. The limits set appear to be reasonable.

3.3.6 Process validation or evaluation

Validation has been demonstrated retrospectively on batches covering the four fill volumes and a range of batch sizes.

Acceptable validation data has also been provided for the environment in which the process occurs.

3.4 Control of excipients

3.4.1 Specification

Sodium chloride, hydrochloric acid, water for injections and nitrogen have monographs in the European Pharmacopoeia. Batch analysis has been provided.

The analytical methods used to test the excipients are those provided in the European Pharmacopoeia. Consequently no validation data has been supplied.

No excipients of human or animal origin have been used in the manufacture of the finished product.

The water for injections is produced on site.

3.5 Control of drug product

3.5.1 Specification

The finished product specification of the product has been supplied and is acceptable.

The specification for shelf-life covers appearance, pH, density, identification, content, related substances, sterility and endotoxins. The limits are the same as those for release with the exception of total unknown impurities.

3.5.2 Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods.

3.5.3 Validation

Relevant analytical methods have been supported by satisfactory validation data.

3.5.4 Reference standards

Suitable information on the reference standards has been provided.

3.5.5 Batch analyses

The specifications are satisfied for all of the batches which are all comparable on the common parameters.

3.5.6 Characterisation of impurities

The potential impurities from the active substance are those listed in the European Pharmacopoeia plus the additional impurities requested by the EDQM.

It has been demonstrated that the analytical test method used for assay of epirubicin and related substances can be used for the impurities listed in the pharmacopoeia.

3.6 Container closure system

The injection vials are type I, colourless, moulded glass and comply with the requirements of the European Pharmacopoeia.

The closures are grey fluoropolymer coated chlorobutyl rubber stoppers. These comply with the requirements of the European Pharmacopoeia.

The metallic cap is aluminium sheet. This item is not in contact with the finished product.

Relevant specifications and quality reports have been supplied from the finished product manufacturer. Drawings have also been supplied.

3.7 Stability

Stability has been conducted on batches of 10mg/5ml, 50mg/25ml, 100mg/50ml and 200mg/100ml. All batches have been stored under long-term and accelerated conditions. In all cases the container closure system is that proposed for commercial use. The vials were orientated upside down during storage to ensure permanent contact of the solution with the stoppers.

All batches stored under long-term conditions remained within specification.

Under accelerated conditions, the product is clearly not stable. There is a decrease in epirubicin content with a corresponding increase in all of the impurities with the product out of specification at 6 months.

Sodium chloride solution 0.9% and glucose 5% have been demonstrated to be suitable infusion fluids. Stability was investigated at concentrations of 1mg/ml and 0.1mg/ml over 28 days stored in the fridge and at room temperature. Infusion solutions with a concentration of 0.1mg/ml were stable for 28 days in the fridge and 4 days at room temperature. At 1mg/ml infusion solutions with glucose are stable for 7 days in the fridge and at room temperature. Whereas 1mg/ml with sodium chloride 0.9% is stable for 28 days in the fridge and 7 days at room temperature. It was also shown that the container of the infusion vehicle has no influence with polyvinylchloride, polypropylene, polyethylene and glass all investigated. The test for leachables was omitted on the basis that the finished product is an aqueous solution with no preservatives, it is therefore considered that epirubicin dissolved in the recommended infusion media will have no more potential for leachables than the recommended infusion media alone.

The applicant is proposing a shelf life of 24 months when stored between 2°C to 8°C, which is supported by the long term stability data. It was demonstrated during development that the product is not photosensitive.

After first opening or following reconstitution the applicant has recommended that the product should be used as soon as possible in line with the guidelines.

3.8 Other information

3.8.1 Biostudy

No new clinical work has been presented on the basis that the product is well known.

3.8.2 Essential similarity

Comparable impurity profiles and levels have been demonstrated for the finished product and Pharmorubicin.

4. PRODUCT LITERATURE

4.1 SPC

In terms of quality the SPC is complete and in compliance with the quality part of the dossier and the SPC guideline.

4.2 PIL

The PIL is in compliance with the SPC and the relevant guidelines and is considered acceptable.

4.3 LABEL

The label is in compliance with the SPC and the relevant guidelines and is considered acceptable.

5. ADMINISTRATIVE

5.1 Quality Overall Summary

The summary has been done by a suitably qualified expert. The report is a summary of the module.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

INTRODUCTION

These are national abridged applications submitted under Article 10.1a (iii) ('essential similarity') of EC Directive 2001/83/EEC.

The applications are made on the basis that epirubicin is a well established cytotoxic agent with well-known efficacy and safety for use in a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinomas as well as malignant lymphomas, leukaemias and multiple myeloma. Intravesical administration is also beneficial in the treatment of papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and the prophylaxis of recurrences after transurethral resection.

The applicant claims that the proposed product, Epirubicin 2mg/ml concentrate for solution for injection or infusion (10mg in 5mL, 50mg in 25mL, 100mg in 50mL and 200mg in 100mL) is essentially similar to the originator product – Pharmorubicin Solution for Injection 2mg/mL, which was authorised to Pharmacia (Farmitalia Carlo Erba) in the UK on 18th January 1991 - PL 03433/0135. No new clinical data have therefore been submitted.

The formulation of CP Pharmaceuticals' product is similar in terms of excipients to Pharmorubicin Solution for Injection 2mg/mL. The impurity profile of the active ingredient in the proposed product complies with the specification proposed. This aspect will be discussed more fully in the Quality AR.
As the formulation is a simple solution for IV injection/infusion there are no issues relating to bioavailability.

GCP aspects

N/A

Orphan Medicinal Products

N/A

CLINICAL PHARMACOLOGY

Pharmacokinetics

There is no reason why the PK of the CP Pharmaceuticals Epirubicin 2mg/ml concentrate should differ from that of the originator product. The information provided in Section 5.2 of the SPC for CPs product is therefore identical to that provided in Section 5.2 for Pharmorubicin.

- **Bioavailability**

The active ingredient in the proposed product, as for Pharmorubicin, is epirubicin hydrochloride. Epirubicin hydrochloride is the subject of a Ph Eur monograph. Evaluation of the epirubicin hydrochloride manufactured by the proposed suppliers showed that all samples tested complied with the Ph Eur specification for related substances.

The epirubicin hydrochloride used in the manufacture of the CP product can therefore be considered chemically equivalent to that used in the manufacture of Pharmorubicin Solution for injection 2mg/mL.

The CP Pharmaceuticals product is also similar in terms of excipients to the originator product.

This aspect will be discussed more fully in the Quality AR.

As the proposed product is to be infused as an aqueous IV solution containing the same active substance in the same concentration as the Pharmorubicin Solution for injection, the product is exempt from the provision of a bioequivalence study in accordance with the Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98) adopted July 2001.

- **Interactions**

As CP Pharmaceuticals' product contains the same active ingredient, epirubicin hydrochloride, as Pharmorubicin solution for injection 2mg/mL, Section 4.5 of the SPC will be identical to that for the originator product.

Pharmacodynamics

For the reasons given above, the PD characteristics of the proposed product are not expected to differ from those of the originator product, Pharmorubicin solution for injection 2mg/mL. The information provide in Section 5.1 of the proposed SPC is, therefore, identical to that provided for Pharmorubicin.

CLINICAL EFFICACY

The efficacy of epirubicin in the treatment of the following conditions is well established:

- a wide range of neoplastic conditions, including breast, ovarian, gastric, lung and colorectal carcinoma, malignant lymphomas, leukaemias and multiple myeloma.
- Papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and the prophylaxis of recurrences after transurethral resection by intravesical administration.

As the CP Pharmaceuticals' preparation is chemically equivalent to Pharmorubicin Solution for Injection 2mg/mL, the therapeutic effect should be the same. Therefore Sections 4.1 and 4.2 of the proposed SPC relating to 'Therapeutic Indications' and 'Posology and Method of Administration' contains identical text to that approved for the

Pharmorubicin solution for injection 2mg/mL (although subheadings have been inserted together with information on use in children, to comply with the EC Guidelines).

CLINICAL SAFETY

Assessor's overall conclusions on clinical safety

The safety of epirubicin in the indications listed above is well established.
Since CP Pharmaceuticals Epirubicin 2mg/mL Concentrate for Solution for Injection or Infusion is chemically equivalent to Pharmorubicin Solution for Injection 2mg/mL, there is no reason to believe the safety profile will differ. Sections 4.3, 4.4, 4.6, 4.7, 4.8 and 4.9 of the SPC for CP Pharmaceuticals products is virtually the same as that of the Pharmorubicin SPC (the terms 'aspartate aminotransferase' and 'alanine transaminase' are used rather than abbreviations and the definition of severe neutropenia has been corrected <500 neutrophils/mm3 for >7 days).

CLINICAL EXPERT

The clinical expert is medically qualified and currently employed as an Independent Consultant (Pharmaceutical Physician).

SPC

This is consistent with the originator product.

PIL

This is satisfactory.

LABEL

This is satisfactory.

CONCLUSIONS

The formulation of CPs Epirubicin 2mg/mL Concentrate for Solution for Injection or Infusion (10mg in 5mL, 50mg in 25mL, 100mg in 50mL and 200mg in 100mL) can be considered essentially similar to Pharmorubicin Solution for Injection 2mg/mL, which has been licensed in the UK for >10 years. The efficacy and safety profiles of the two products would therefore be expected to be equivalent.

The therapeutic indications given in the CP product's SPC are conventional and in line with those approved for Pharmorubicin Solution for Injection 2mg/mL and with current medical opinion.

There is no reason why the benefit-risk ratio for CP Pharmaceuticals Epirubicin 2mg/mL Concentrate for Solution for Injection should differ from that of the originator product Pharmorubicin Solution for Injection 2mg/mL.

Marketing authorisation can therefore be recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Epirubicin is a well known cytotoxic agent and has been used for many years to produce responses in a wide range of neoplastic conditions. The applicant has demonstrated essential similarity to the originator product, Pharmorubicin 2mg/ml concentrate for solution for injection or infusion.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and the originator product are interchangeable. Extensive clinical experience with epirubicin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0491-4

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 04/06/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 29/06/2004.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 08/03/2005 and 19/08/2005.
4	The applicant responded to the MHRA's requests, providing further information on 23/06/2005 and 10/11/2005.
5	The application was determined on 23/02/2006.

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0491-4

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0491

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg of epirubicin hydrochloride

Each 5ml vial contains 10mg of epirubicin hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion

Clear, red solution, free of particles

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 papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Intravenous Administration:

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.
Adults and the elderly

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 I.V. over three to five minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in the case of liver impairment.

High doses:

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

• Small cell lung cancer (previously untreated): 120 mg/m^2 day one, every three weeks.

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

The drug should be given as an I.V. bolus over three to five 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 by neoplastic bone-marrow infiltration. The total dose per cycle may be divided over two to three successive days.

Combination therapy:

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced.

Hepatic impairment:

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/100 ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Renal impairment:

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 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.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml 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 one 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.

Children:

Not recommended, due to lack of data on use in children.

4.3 Contraindications

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is contraindicated in patients with marked myelosuppression induced by previous treatment with other anti-tumour 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 2mg/ml Concentrate for Solution for Injection or Infusion should be administered only under the supervision of qualified physicians experienced in antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion 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 2mg/ml Concentrate for Solution for Injection or Infusion, 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 (aspartate transaminase, alanine transaminase, 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 cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart 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 2mg/ml Concentrate for Solution for Injection or Infusion may impart a red colour to the urine for one to two days after administration.

This medicinal product contains 0.77mmol of sodium in each vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion be mixed with other drugs (see Section 6.2 Incompatibilities). However, Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion can be used in combination with other anti-cancer drugs.

Cimetidine increases formation of the active metabolite of epirubicin and exposure to 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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions have been described:

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

• Mucositis may appear five to ten 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.

• Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.

• Hyperpyrexia.

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

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.

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

Haematologic:

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 (one to three year) latency period.

4.9 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 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 six 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

ATC Code - L01DB03
ATC Group - Antineoplastic agents, cytotoxic antibiotics and related substances

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).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. 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 1/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

No further information is given.

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

Two years – unopened

After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4 Special precautions for storage

Store at 2-8°C.

Keep container in the outer carton

After dilution:-

Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%

Chemical and physical in use stability has been demonstrated for seven days at 25°C.

Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and seven days at 25°C.

Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and four days 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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Colourless Type I glass vial with a nominal capacity of 5ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 vial containing 5ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

6.6 Special precautions for disposal

Epirubicin 2mg/mlConcentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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

• Personnel should be trained in good technique for handling.

• Pregnant staff should be excluded from working with this drug.

• Personnel handling Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.

• All items used for 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. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd

Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0491

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2006

10 DATE OF REVISION OF THE TEXT

23/02/2006

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0492

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg of epirubicin hydrochloride
Each 25ml vial contains 50mg of epirubicin hydrochloride
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion
Clear, red solution, free of particles

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 papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Intravenous Administration:

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Adults and the elderly

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 I.V. over three to five minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in the case of liver impairment.

High doses:

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

. • Small cell lung cancer (previously untreated): 120 mg/m^2 day one, every three weeks.
. • Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day one or 45 mg/m^2 day one, two, three every three weeks.

The drug should be given as an I.V. bolus over three to five 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 by neoplastic bone-marrow infiltration. The total dose per cycle may be divided over two to three successive days.
Combination therapy:

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced.
Hepatic impairment:

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/100 ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Renal impairment: 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 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.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml 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 one 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.

Children:

Not recommended, due to lack of data on use in children.

4.3 Contraindications

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is contraindicated in patients with marked myelosuppression induced by previous treatment with other anti-tumour 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 2mg/ml Concentrate for Solution for Injection or Infusion should be administered only under the supervision of qualified physicians experienced in

antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion 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 2mg/ml Concentrate for Solution for Injection or Infusion, 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 (aspartate transaminase, alanine transaminase, 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 cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart 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 2mg/ml Concentrate for Solution for Injection or Infusion may impart a red colour to the urine for one to two days after administration.

This medicinal product contains 3.85mmol of sodium in each vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion be mixed with other drugs (see Section 6.2 Incompatibilities). However, Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion can be used in combination with other anti-cancer drugs.
Cimetidine increases formation of the active metabolite of epirubicin and exposure to 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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions have been described:

- Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
- Mucositis may appear five to ten 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.
- Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.
- Hyperpyrexia.

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

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

Haematologic:

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 (one to three year) latency period.

4.9 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 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 six 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

ATC Code - L01DB03 ATC Group - Antineoplastic agents, cytotoxic antibiotics and related substances

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).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern

with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. 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 1/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

No further information is given.

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

Two years – unopened

After dilution, see section 6.4 Special precautions for storage.
Discard any unused solution immediately after use.

6.4 Special precautions for storage

Store at 2-8°C.
Keep container in the outer carton.

After dilution:-

Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%

Chemical and physical in use stability has been demonstrated for seven days at 25°C.

Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and seven days at 25°C.

Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and four days 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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Colourless Type I glass vial with a nominal capacity of 50ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 vial containing 25ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

6.6 Special precautions for disposal

Epirubicin 2mg/mlConcentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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

. • Personnel should be trained in good technique for handling.
. • Pregnant staff should be excluded from working with this drug.
. • Personnel handling Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.
. • All items used for 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. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0492

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2006

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0493

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg of epirubicin hydrochloride
Each 50ml vial contains 100mg of epirubicin hydrochloride
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion
Clear, red solution, free of particles

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 papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Intravenous Administration:

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Adults and the elderly

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 I.V. over three to five minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in the case of liver impairment.

High doses:

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

. • Small cell lung cancer (previously untreated): 120 mg/m^2 day one, every three weeks.
. • Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day one or 45 mg/m^2 day one, two, three every three weeks.

The drug should be given as an I.V. bolus over three to five 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 by neoplastic bone-marrow infiltration. The total dose per cycle may be divided over two to three successive days.
Combination therapy:

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced.
Hepatic impairment:

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/100 ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Renal impairment: 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 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.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml 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 one 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.

Children:

Not recommended, due to lack of data on use in children.

4.3 Contraindications

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is contraindicated in patients with marked myelosuppression induced by previous treatment with other anti-tumour 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 2mg/ml Concentrate for Solution for Injection or Infusion should be administered only under the supervision of qualified physicians experienced in

antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion 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 2mg/ml Concentrate for Solution for Injection or Infusion, 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 (aspartate transaminase, alanine transaminase, 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 cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart 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 2mg/ml Concentrate for Solution for Injection or Infusion may impart a red colour to the urine for one to two days after administration.

This medicinal product contains 3.85mmol of sodium in each vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion be mixed with other drugs (see Section 6.2 Incompatibilities). However, Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion can be used in combination with other anti-cancer drugs.
Cimetidine increases formation of the active metabolite of epirubicin and exposure to unchanged epirubicin by pharmacokinetic interaction.

4.7 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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions have been described:

- Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
- Mucositis may appear five to ten 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.
- Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.
- Hyperpyrexia.

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

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

Haematologic:

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 (one to three year) latency period.

4.10 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 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 six 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

5.2 Pharmacodynamic properties

ATC Code - L01DB03 ATC Group - Antineoplastic agents, cytotoxic antibiotics and related substances

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).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern

with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. 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 1/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

No further information is given.

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

Two years – unopened

After dilution, see section 6.4 Special precautions for storage.
Discard any unused solution immediately after use.

6.4 Special precautions for storage

Store at 2-8°C.
Keep container in the outer carton.

After dilution:-

Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%

Chemical and physical in use stability has been demonstrated for seven days at 25°C.

Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and seven days at 25°C.

Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and four days 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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Colourless Type I glass vial with a nominal capacity of 50ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 vial containing 50ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

6.6 Special precautions for disposal

Epirubicin 2mg/mlConcentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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

. • Personnel should be trained in good technique for handling.
. • Pregnant staff should be excluded from working with this drug.
. • Personnel handling Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.
. • All items used for 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. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0493

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2006

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0494

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg of epirubicin hydrochloride
Each 100ml vial contains 200mg of epirubicin hydrochloride
For excipients, see 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion
Clear, red solution, free of particles

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 papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2 Posology and method of administration

Intravenous Administration:

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Adults and the elderly

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 I.V. over three to five minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in the case of liver impairment.

High doses:

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

. • Small cell lung cancer (previously untreated): 120 mg/m^2 day one, every three weeks.
. • Non-small cell lung cancer (squamous, large cell, and adenocarcinoma previously untreated): 135 mg/m^2 day one or 45 mg/m^2 day one, two, three every three weeks.

The drug should be given as an I.V. bolus over three to five 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 by neoplastic bone-marrow infiltration. The total dose per cycle may be divided over two to three successive days.
Combination therapy:

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced.
Hepatic impairment:
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/100

ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Renal impairment: 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 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.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml 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 one 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.

Children:

Not recommended, due to lack of data on use in children.

4.3 Contraindications

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is contraindicated in patients with marked myelosuppression induced by previous treatment with other anti-tumour 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 2mg/ml Concentrate for Solution for Injection or Infusion should be administered only under the supervision of qualified physicians experienced in antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion 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 2mg/ml Concentrate for Solution for Injection or Infusion, 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 (aspartate transaminase, alanine transaminase, 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 cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart 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 2mg/ml Concentrate for Solution for Injection or Infusion may impart a red colour to the urine for one to two days after administration.

This medicinal product contains 3.85mmol of sodium in each vial. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion be mixed with other drugs (see Section 6.2 Incompatibilities). However, Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion can be used in combination with other anti-cancer drugs.
Cimetidine increases formation of the active metabolite of epirubicin and exposure to unchanged epirubicin by pharmacokinetic interaction.

4.8 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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions have been described:

- Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
- Mucositis may appear five to ten 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.
- Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.
- Hyperpyrexia.

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

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.

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

Haematologic:

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 (one to three year) latency period.

4.11 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 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 six 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

5.3 Pharmacodynamic properties

ATC Code - L01DB03 ATC Group - Antineoplastic agents, cytotoxic antibiotics and related substances

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).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in

terms of plasma clearance values and metabolic pathway. 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 1/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

No further information is given.

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

Two years – unopened

After dilution, see section 6.4 Special precautions for storage.
Discard any unused solution immediately after use.

6.4 Special precautions for storage

Store at 2-8°C.
Keep container in the outer carton.

After dilution:-

Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%

Chemical and physical in use stability has been demonstrated for seven days at 25°C.

Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and seven days at 25°C.

Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%

Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and four days 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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Colourless Type I glass vial with a nominal capacity of 50ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.

Packs of 1 vial containing 25ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

6.6 Special precautions for disposal

Epirubicin 2mg/mlConcentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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

. • Personnel should be trained in good technique for handling.
. • Pregnant staff should be excluded from working with this drug.
. • Personnel handling Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.
. • All items used for 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. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0494

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/02/2006

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION - PL 04543/0491-4

TECHNICAL LEAFLET

PACKAGE LEAFLET

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion
Epirubicin hydrochloride

Read all of this leaflet carefully before you are given this medicine.
Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or nurse.

In this leaflet:

The active substance in the injection is epirubicin hydrochloride. 1ml of solution contains 2mg of epirubicin hydrochloride.

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

Epirubicin 2mg/ml Concentrate for Solution for Infusion is manufactured by EBEWE Pharma Ges.m.b.H. Nfg. KG, A-4866 Unterach, Austria for the Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF.

1. WHAT IS EPIRUBICIN CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION AND WHAT IS IT USED FOR?

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is a concentrated form of epirubicin which must be diluted before use. It is available in packs of 1 vial.

Each 5ml vial contains 10mg of epirubicin hydrochloride.
Each 25ml vial contains 50mg of epirubicin hydrochloride
Each 50ml vial contains 100mg of epirubicin hydrochloride
Each 100ml vial contains 200mg of epirubicin hydrochloride

Epirubicin 2mg/ml concentrate for solution for injection or infusion is a clear, red solution free from particles.

Epirubicin belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer. Epirubicin may be used to treat a wide range of cancers including breast, ovarian, gastric, lung, bladder and colorectal, malignant lymphomas, leukaemias and multiple myeloma.

2. BEFORE YOU ARE GIVEN EPIRUBICIN CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

You will not be given Epirubicin Concentrate for Solution for Injection for Infusion:

- if you are allergic to epirubicin or any of the other ingredients
- if you have a very low level of white blood cells in your blood due to previous treatment with other cytotoxic drugs or recent radiotherapy
- if you have been given the maximum dose of doxorubicin or daunorubicin (other cytotoxic drugs)
- if you have or have had previously had heart problems
- if you are pregnant, breast-feeding or trying for a baby

Your doctor will take special care when giving you epirubicin:

- if you have liver problems. Your dose may have to be reduced.
- Are you supposed to control the amount of sodium in your diet? You should be aware that this medicine contains sodium chloride and that the amount of sodium is 0.77mmol in the 5ml vial, 3.85mmol in the 25ml vial, 7.70mmol in the 50ml vial and 15.40mmol in the 100ml vial. Please ask your doctor or nurse for advice about your sodium intake while you are having epirubicin.

Consult your doctor if any of the above warnings applies to you or has applied to you in the past.

Your doctor will also check your blood, liver and heart before, during and after every treatment. If the results of any of these tests are abnormal treatment will only be resumed when all readings are back to normal.

Pregnancy

Epirubicin should not be given to you if you are pregnant, because it can cause serious birth defects.

Female patients should also avoid getting pregnant while being treated with epirubicin and for at least six months afterwards. Male patients receiving epirubicin should take adequate precautions to ensure that their partner does not

become pregnant for the same period. If you are considering becoming parents after the treatment, you should discuss this with your doctor.

Men who wish to father children in the future should seek advice about freezing sperm before the epirubicin treatment is started.

Breast-feeding

Epirubicin should not be given to you if you are breast-feeding, as epirubicin might pass into breast milk and affect the baby.

Driving and using machines:

Epirubicin treatment should not affect your ability to drive, but if you feel unwell, you should not drive or operate machinery.

Being given epirubicin at the same time as other medication

Epirubicin is often used in combination with other cytotoxic drugs.

Care is required if epirubicin is administered at the same time as cimetidine, a drug used for stomach ulcers.

Tell your doctor or pharmacist about medicines you are currently taking or have taken recently. This also applies to medicines you may have bought yourself from a pharmacy or supermarket.

3. HOW EPIRUBICIN CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION WILL BE GIVEN TO YOU

Epirubicin Concentrate for Solution for Injection or Infusion will only be given to you under the supervision of a doctor specialised in this type of treatment.

The dosage of epirubicin depends on the condition you are being treated for, your response to the therapy and other medication you are being given. The epirubicin concentrate should be diluted before use with a solution of sodium chloride or glucose and given as an injection or infusion (drip) into a vein. **IT SHOULD NOT BE INJECTED INTO THE MUSCLE OR SPINE.**

The usual dosage of epirubicin is 60-90mg per square metre of body surface area, given by injection over three to five minutes at 21 days intervals.

In the treatment of small cell lung cancer, a higher dose of 120 mg per square metre of body surface area is given by injection over three to five minutes, or by infusion over 20-30 minutes, every three weeks. In the treatment of non-small cell lung cancer, is the usual dose is 135mg per square metre of body surface area given by injection over three to five minutes or by infusion over 20-30 minutes every three weeks. Alternatively,three daily doses of 45mg per square metre of body surface area can be given by injection over three to five minutes, or by infusion over 20-30 minutes, every three weeks.

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

Epirubicin can also be given directly into the bladder to treat bladder cancer or to stop recurrence after bladder surgery to remove the cancer. The dose will depend upon the type of bladder cancer.

Your general condition and your response to the treatment will be closely observed before, during and after the epirubicin treatment.

4. POSSIBLE SIDE EFFECTS

Like any other medication, epirubicin may cause side-effects.

These include temporary hair loss and lack of beard growth in males, nausea, vomiting, diarrhoea, constipation, and sore mouth or tongue (usually five to ten days after the start of treatment). Patients treated for bladder cancer may experience a burning sensation when passing water (urine) or notice a little blood in the urine.

Epirubicin Concentrate is a red solution. You may notice this red colour when you pass water for up to two days. This is normal and nothing to worry about.

As well as killing the cancer cells, the medicine may also affect some of your own cells especially the cells in your blood. This may make you anaemic or prone to infections or to bleeding or bruising easily. If you think you have an infection, a sore throat, mouth ulcers, fever, chills or achiness you should contact your doctor.

Rarely, patients have developd leukaemia some time after being given epirubicin together with other cytotoxic drugs.

Pain may occur temporarily at the injection site.

Allergic reactions to epirubicin can occur, with wheezing, a skin rash or swelling of your lips, eyes or tongue. You should contact your doctor **immediately** if you develop such symptoms.

Epirubicin can harm unborn babies (see section on pregnancy). It may also affect fertility in men and women.

If you get any epirubicin in your eyes you should rinse with lots of water and tell your doctor or nurse immediately.

If you notice any side-effects not mentioned in this leaflet, please tell your doctor or nurse.

5. STORING EPIRUBICIN

Keep out of the reach and sight of children
Store in a refrigerator
Do not use after the expiry date stated on the label.
After dilution, Chemical and physical in use stability has been demonstrated for seven days at 25°C.(Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%), 28 days at 2-8°C and seven days at 25°C (Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%) and 28 days at 2-8°C and four days at 25°C (Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%)
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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

This leaflet was prepared in October 2005

.....

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2mg of epirubicin hydrochloride

Each 5ml vial contains 10mg of epirubicin hydrochloride
Each 25ml vial contains 50mg of epirubicin hydrochloride
Each 50ml vial contains 100mg of epirubicin hydrochloride
Each 100ml vial contains 200mg of epirubicin hydrochloride

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion

Clear, red solution, free of particles

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 papillary transitional cell carcinoma of the bladder, carcinoma-in-situ and in the prophylaxis of recurrences after transurethral resection.

4.2. Posology and method of administration

Intravenous Administration:

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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 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. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Adults and the elderly

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 I.V. over three to five minutes and, depending on the patient's haematomedullary status, the dose should be repeated at 21-day intervals.

Dose modification (reduction) following signs of toxicity (specifically severe neutropenia/neutropenic fever and thrombocytopenia, which could persist on Day 21 after the first dose) could be required or the following dose could be delayed, as in the case of liver impairment.

High doses:

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

- Small cell lung cancer (previously untreated): 120 mg/m^2 day one, every three weeks.

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

The drug should be given as an I.V. bolus over three to five 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 by neoplastic bone-marrow infiltration. The total dose per cycle may be divided over two to three successive days.

Combination therapy:

When the drug is used in combination with other anti-tumour agents, the doses need to be adequately reduced.

Hepatic impairment:

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/100 ml) requires a 50% reduction of dose, while severe impairment > 3mg/100 ml) necessitates a dose reduction of 75%.

Renal impairment:

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 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.

While many regimens have been used, the following may be helpful as a guide: for therapy, 8 x weekly instillations of 50 mg/50ml (diluted with saline or distilled sterile water). In the case of local toxicity (chemical cystitis), a dose reduction to 30 mg/50ml 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 one 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.

Children:

Not recommended, due to lack of data on use in children.

4.3. Contraindications

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion is contraindicated in patients with marked myelosuppression induced by previous treatment with other anti-tumour 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 2mg/ml Concentrate for Solution for Injection or Infusion should be administered only under the supervision of qualified physicians experienced in antiblastic and cytotoxic therapy. Treatment with high dose Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion 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 2mg/ml Concentrate for Solution for Injection or Infusion, 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 (aspartate transaminase, alanine transaminase, 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 cardiac toxicity may occur rarely below this range. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart 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 2mg/ml Concentrate for Solution for Injection or Infusion may impart a red colour to the urine for one to two days after administration.

This medicinal product contains 0.77mmol of sodium in each 5ml vial, 3.85mmol in each 25ml vial, 7.70mmol in each 50ml vial and 15.40mmol in each 100ml vial. To be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion be mixed with other drugs (see Section 6.2 Incompatibilities). However, Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion can be used in combination with other anti-cancer drugs.

Cimetidine increases formation of the active metabolite of epirubicin and exposure to 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

There have been no reports of particular adverse events relating to effects on ability to drive and to use machines.

4.8 Undesirable effects

Apart from myelosuppression and cardiotoxicity, the following adverse reactions have been described:

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

• Mucositis may appear five to ten 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.

• Gastro-intestinal disturbances, such as nausea, vomiting and diarrhoea.

• Hyperpyrexia.

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

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.

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

Haematologic:

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 (one to three year) latency period.

4.9. Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 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 six months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines.

PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code - L01DB03
ATC Group - Antineoplastic agents, cytotoxic antibiotics and related substances

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 SAI8O (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 intravenous injection of 60-150 mg/m^2 of the drug follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. 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**

No further information is given.

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**

Two years –unopened
After dilution, see section 6.4 Special precautions for storage.

Discard any unused solution immediately after use.

6.4. **Special precautions for storage**

Store at 2-8°C.
Keep container in the outer carton.

After dilution:-

Epirubicin 1mg/ml Infusion Solution Prepared with Glucose 5%
Chemical and physical in use stability has been demonstrated for seven days at 25°C.

Epirubicin 1mg/ml Infusion Solution Prepared with Sodium Chloride 0.9%
Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and seven days at 25°C.

Epirubicin 0.1mg/ml Infusion Solution Prepared with Glucose 5% or Sodium Chloride 0.9%
Chemical and physical in use stability has been demonstrated for 28 days at 2-8°C and four days 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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.

6.5. **Nature and contents of container**

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (10mg in 5ml):-

Colourless Type I glass vial with a nominal capacity of 5ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.
Packs of 1 vial containing 5ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (50mg in 25ml):-

Colourless Type I glass vial with a nominal capacity of 50ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.
Packs of 1 vial containing 25ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (100mg in 50ml):-

Colourless Type I glass vial with a nominal capacity of 50ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.
Packs of 1 vial containing 50ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (200mg in 100ml):-

Colourless Type I glass vial with a nominal capacity of 100ml with fluropolymer-coated chlorobutyl rubber stoppers and aluminium overseal.
Packs of 1 vial containing 100ml of Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion.

6.6. Instructions for use and handling

Epirubicin 2mg/mlConcentrate for Solution for Injection or Infusion should be diluted before use with 0.9% sodium chloride or 5% glucose solutions.

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

- Personnel should be trained in good technique for handling.

- Pregnant staff should be excluded from working with this drug.

- Personnel handling Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion should wear protective clothing: goggles, gowns and disposable gloves and masks.

- All items used for 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. Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham
LL13 9UF
UK

7. MARKETING AUTHORISATION NUMBER

Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (10mg in 5ml) – PL 04543/0491
Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (50mg in 25ml) – PL 04543/0492
Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (100mg in 50ml) – PL 04543/0493
Epirubicin 2mg/ml Concentrate for Solution for Injection or Infusion (200mg in 100ml) – PL 04543/0494

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

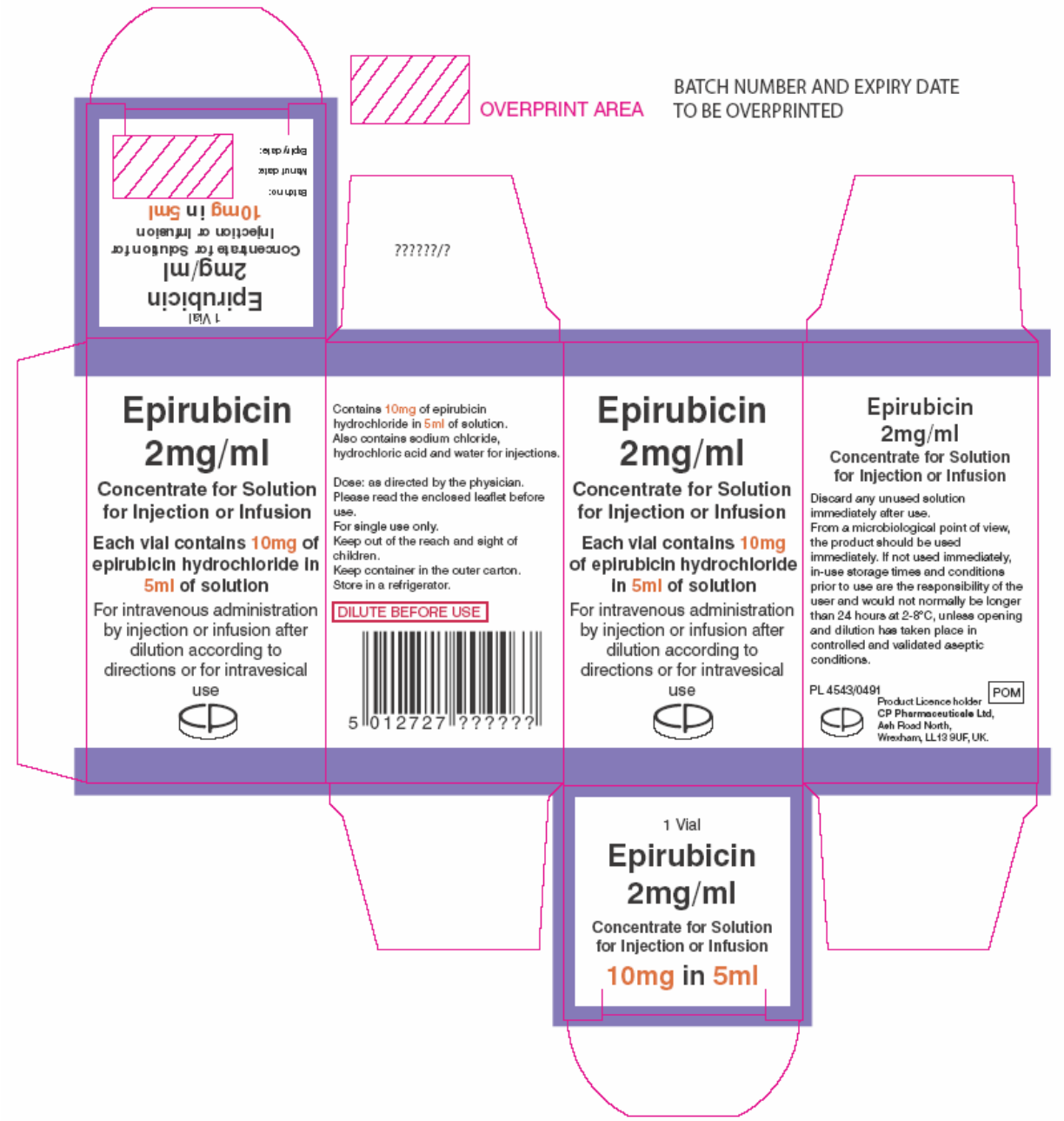
20th October 05

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

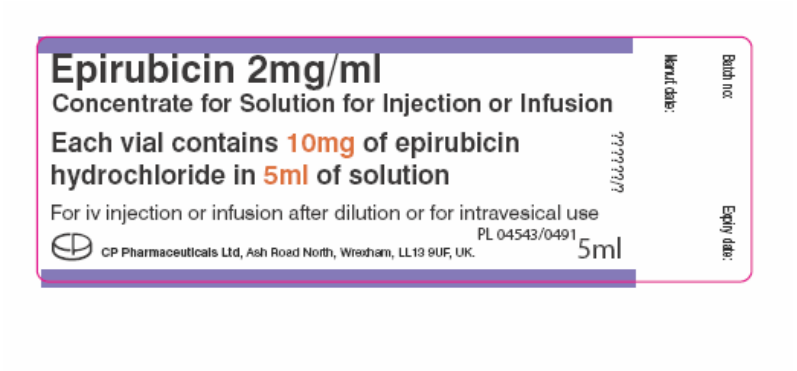
PL 04543/0491

LABELLING

CARTON



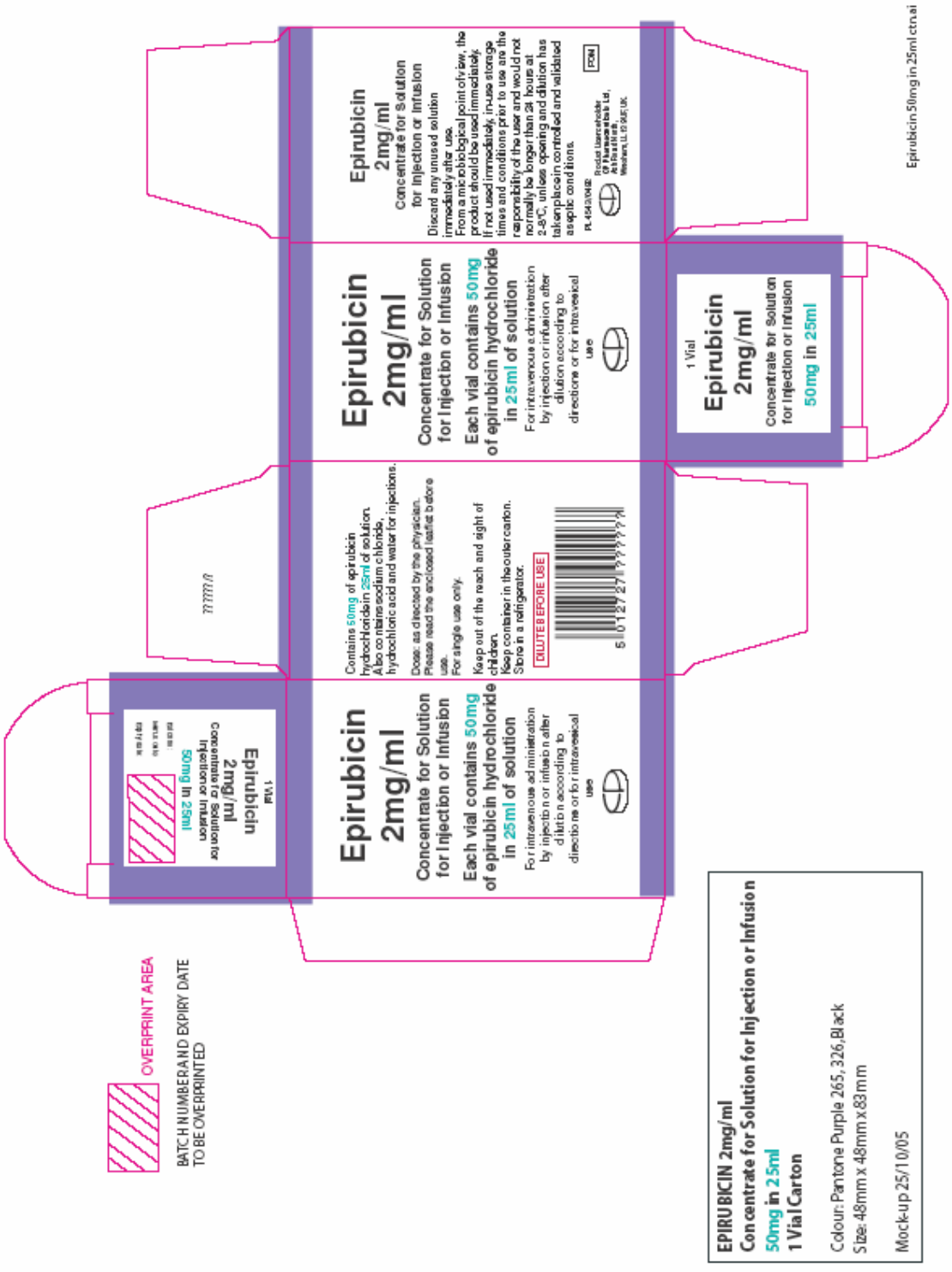
LABEL


Epirubicin 2mg/ml
Concentrate for Solution for Injection or Infusion
Each vial contains 10mg of epirubicin hydrochloride in 5ml of solution
For iv injection or infusion after dilution or for intravesical use
PL 04543/0491
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
5ml
Manuf date:
Batch no:
Expiry date:

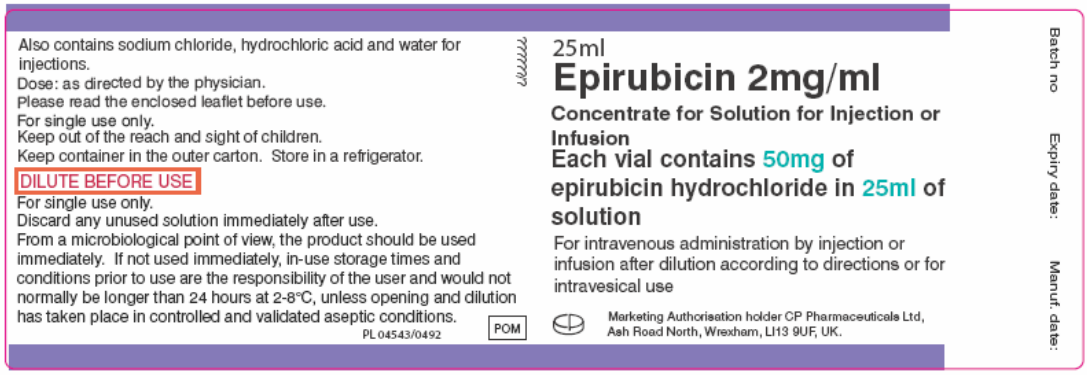
EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0492

CARTON



LABEL



100%

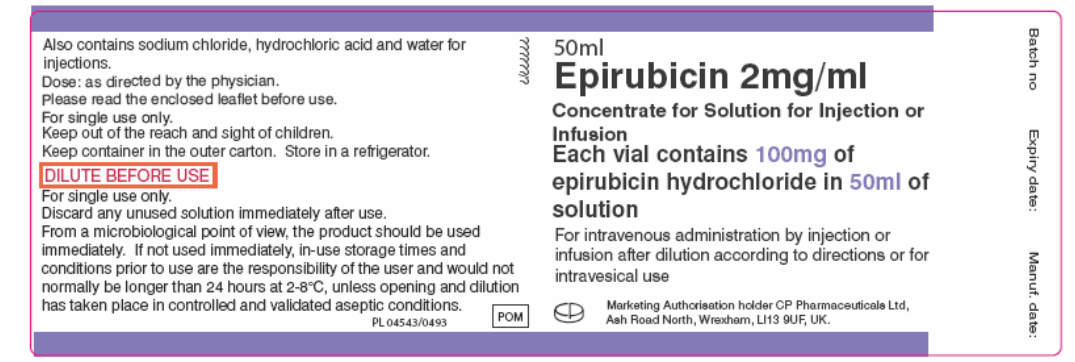
Batch number and expiry date to be overprinted

EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0493

CARTON

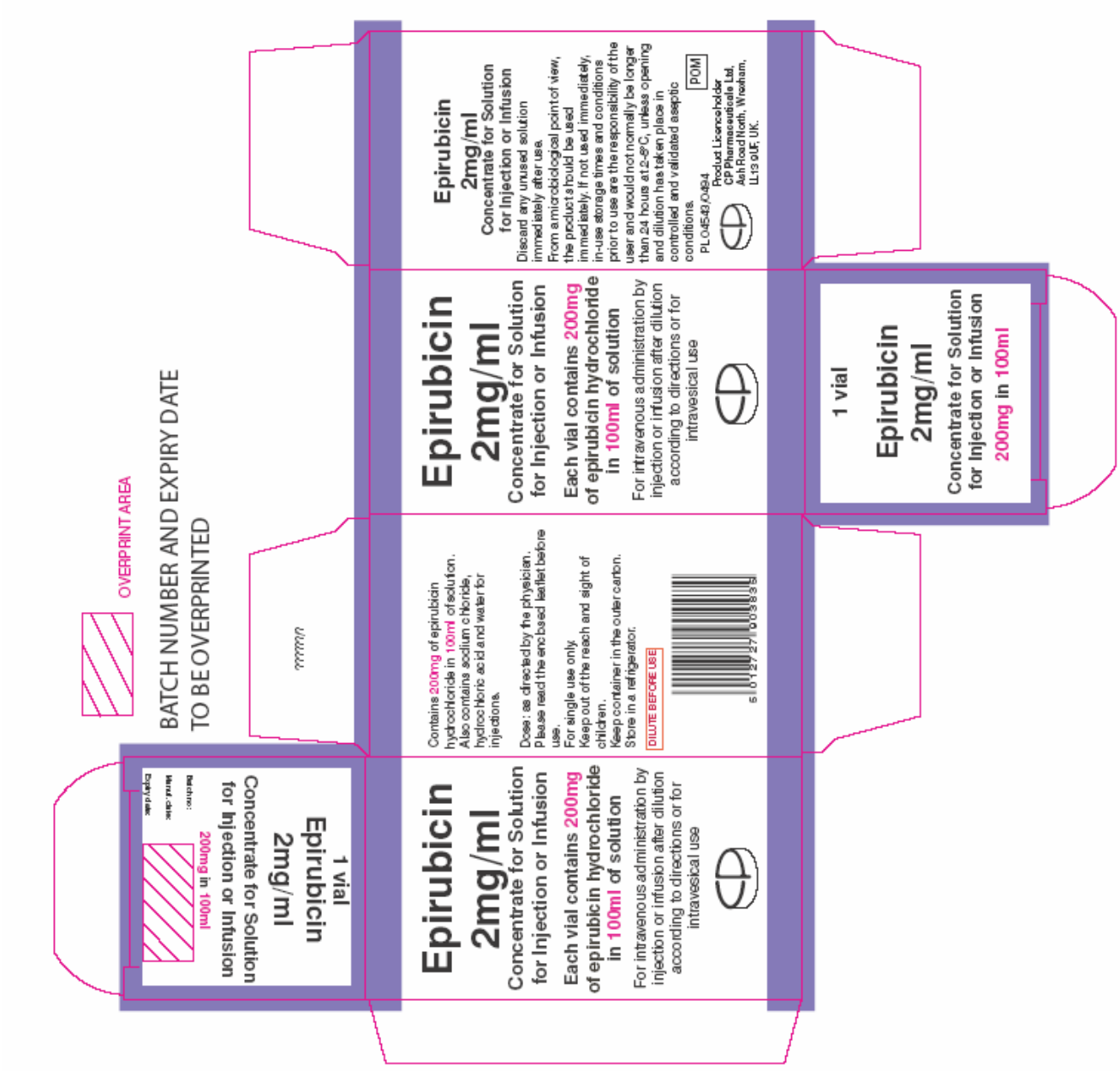
LABEL


Also contains sodium chloride, hydrochloric acid and water for injections.
Dose: as directed by the physician.
Please read the enclosed leaflet before use.
For single use only.
Keep out of the reach and sight of children.
Keep container in the outer carton. Store in a refrigerator.
DILUTE BEFORE USE
For single use only.
Discard any unused solution immediately after use.
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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.
PL 04543/0493
POM
50ml
Epirubicin 2mg/ml
Concentrate for Solution for Injection or Infusion
Each vial contains 100mg of epirubicin hydrochloride in 50ml of solution
For intravenous administration by injection or infusion after dilution according to directions or for intravesical use
Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK.
Batch no
Expiry date:
Manuf. date:

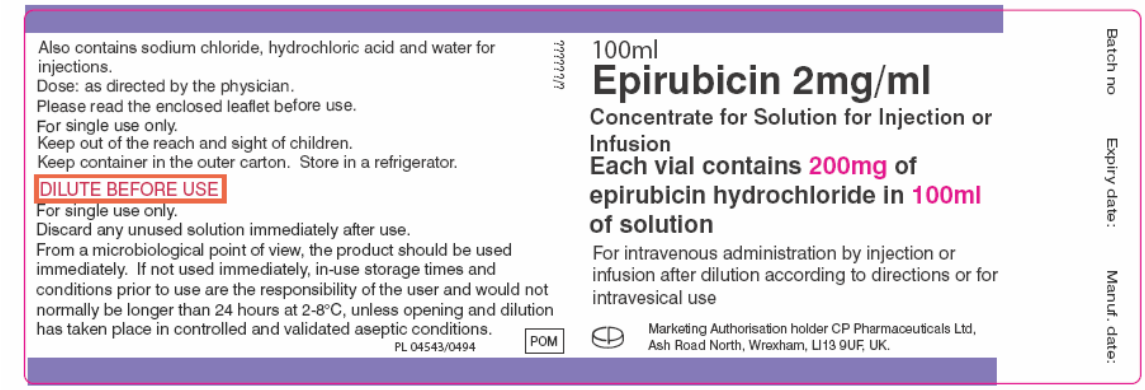
EPIRUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INJECTION OR INFUSION

PL 04543/0494

CARTON



LABEL


Also contains sodium chloride, hydrochloric acid and water for injections.
Dose: as directed by the physician.
Please read the enclosed leaflet before use.
For single use only.
Keep out of the reach and sight of children.
Keep container in the outer carton. Store in a refrigerator.
DILUTE BEFORE USE
For single use only.
Discard any unused solution immediately after use.
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 not normally be longer than 24 hours at 2-8°C, unless opening and dilution has taken place in controlled and validated aseptic conditions.
PL 04543/0494
POM
100ml
Epirubicin 2mg/ml
Concentrate for Solution for Injection or Infusion
Each vial contains 200mg of epirubicin hydrochloride in 100ml of solution
For intravenous administration by injection or infusion after dilution according to directions or for intravesical use
Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LI13 9UF, UK.
Batch no
Expiry date:
Manuf. date: