DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE) 50MG IN 25ML

PL 04543/0471

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE) 10MG IN 5ML

PL 04543/0476

UKPAR

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DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471 & PL 04543/0476

LAY SUMMARY

The MHRA granted CP Pharmaceuticals Limited Marketing Authorisations (licences) on the 28th June 2006, for Doxorubicin 2mg/ml, concentrate for solution for infusion, 10mg in 5ml and 50mg in 25ml. These Prescription Only Medicines (POM) are used to treat a wide range of neoplastic conditions.

Doxorubicin 2mg/ml concentrate for solution for infusion contains the active ingredient doxorubicin hydrochloride, which is a cytotoxic agent.

The clinical data presented to the MHRA, pre licensing, demonstrated that Doxorubicin 2mg/ml concentrate for solution for infusion is essentially similar or equivalent to the approved product, Doxorubicin Solution for Injection 2 mg/ml (PL 03433/0127) and, as such, can be used interchangeably.

No new or unexpected safety concerns arose from these applications. It was therefore judged that the benefits of taking Doxorubicin 2mg/ml concentrate for solution for infusion outweigh the risks. Hence Marketing Authorisations have been granted.

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471 & PL 04543/0476

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for Doxrubicin 2mg/ml concentrate for solution for infusion (10mg in 5ml, and 50mg in 25ml) to CP Pharmaceuticals Limited on 28th June 2006. The product is a Prescription Only Medicine (POM)

The applications were submitted as abridged applications according to article 10a [formerly article 10.1(a) (iii)] of Directive 2001/83/EC as amended, claiming essential similarity to the approved product, Doxorubicin solution for injection 2mg/ml (PL 03433/0127).

The product contains the active ingredient doxorubicin hydrochloride and is indicated in the treatment of a range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas. Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

Although the exact mechanism of action is not yet known, the tumour cells are probably killed through drug-induced alterations of nucleic acid synthesis.
The proposed mechanism of action include the following:
DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrum and cardiolipin).

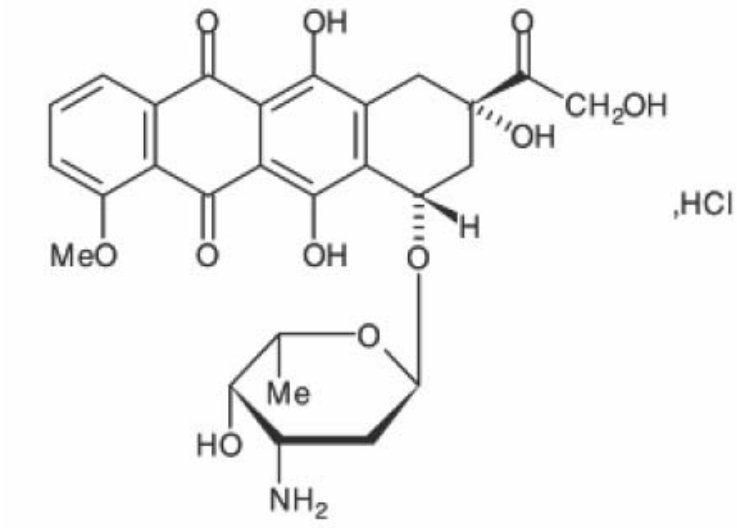
PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

These are standard abridged applications for Marketing Authorisation in the UK submitted under Directive 2001/83/EC, Art 10a [formerly paragraph 1(a)(iii)]. Doxorubicin 2 mg/ml Injection BP is a concentrate for solution for infusion presented in single clear glass vials containing 10 mg in 5 ml and 50 mg in 25 ml of Doxorubicin Hydrochloride Ph Eur. Essential similarity has been claimed to PL 03433/0127, Doxorubicin Solution for Injection 2 mg/ml, granted to Pharmacia & Upjohn in November 1989.
Doxorubicin is an antimitotic and cytotoxic, and has been used successfully to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas. Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent. The recommended dosage regimen is 60-75 mg/m^2 body surface administered as a single intravenous infusion at 3-week intervals. The dosage is considerably reduced in combination chemotherapy and due to factors such as liver dysfunction, previous treatment with other anti-tumour agents or radiotherapy.

2. DRUG SUBSTANCE

Doxorubicin Hydrochloride is 5,12-Naphthacenedione,10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,7,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-,hydrochloride (8S-cis)-; *or* (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycoloyl-7,8,s,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride.



C27H29NO11HCl Mwt = 579.9 (Base = 543.5) *CAS No*: *25316-40-9*

A Ph Eur Certificate of Suitability has been provided for the proposed source of the active ingredient. A letter of access authorising use of the Certificate in support of PLs 04543/0471 and 0476 has been provided.

A copy of the applicant's 'Open' part of the DMF has been included in the Dossier submitted. The active ingredient manufacturer has stated that the manufacturing process does not employ any raw materials that are of bovine, ovine or caprine origin from countries with recorded BSE or scrapie.

Doxorubicin from this source has not previously been approved for use in any medicinal products on the UK market.

The proposed 'in house' Drug Substance Specification (DSS) is consistent with the active ingredient manufacturer's specification for the bulk drug material, that is based on the corresponding USP and Ph Eur monographs.

Proposed routine control test methods carried out on incoming batches of bulk drug material by the proposed finished product manufacturer have been confirmed.

Particle size is not a concern since Doxorubicin Hydrochloride is in solution in the proposed product.

Satisfactory batch analytical data presented by the active ingredient manufacturer

Satisfactory stability data under long-term and accelerated ICH conditions have been provided and support the proposed 2 year retest period.

3. DOSAGE FORM

COMPOSITION

The product is presented as a clear, blood red sterile solution in single clear Type I glass vials with grey fluoropolymer-coated rubber stoppers and aluminium crimp caps. Two fill volumes are proposed: 5 ml and 25 ml. The qualitative composition of the proposed product is summarised in Table 1.

Table 1 – Qualitative composition of Doxorubicin 2 mg/ml Injection BP

Ingredients	**Reference Standard**
Doxorubicin Hydrochloride	Ph Eur
Sodium Chloride	Ph Eur
Dilute Hydrochloric Acid (10%)	Ph Eur
Water for Injections	Ph Eur
Nitrogen	Ph Eur

CLINICAL TRIAL FORMULATION

Not applicable.

PHARMACEUTICAL DEVELOPMENT

Aqueous solutions of Doxorubicin are sensitive to heat and light.

The proposed product is presented as 50 mg/25-ml vial and 10 mg/5-ml vial in colourless Type I glass vials. Compatibility with the container and closure has been reviewed as part of the stability studies undertaken on the finished product.

Stability and compatibility of the proposed doxorubicin concentrate for infusion and commonly used infusion diluents, 5% Dextrose Injection and 0.9% Sodium Chloride Injection were tested at 20-25^{o}C (with and without light protection) and at 2-8° C (protected from light). No physico-chemical incompatibilities were reported and the diluted solutions were stable for up to 24 hours.

MANUFACTURE/PROCESS VALIDATION

GMP Statement
A current manufacturer's authorisation for the proposed site of manufacture, assembly and batch release has been presented to confirm the satisfactory GMP status. The proposed finished product manufacturer has been approved for the manufacture of other parenteral products marketed in the UK.

Manufacturing Process
Typical batch sizes have been stated.
The proposed manufacturing process has been adequately summarised and a satisfactory flow diagram presented.

Satisfactory in-process controls have been provided.
Sterilisation

The sterilisation procedures were satisfactorily validated in accordance with Ph Eur requirements.

Process Validation
Satisfactory process validation data weresupplied for full-scale production batches of both 5ml and 25ml vials.

Satisfactory batch analytical data reported for full-scale production batches of each of the proposed 5-ml and 25-ml vial sizes, manufactured between January and March 2001 by the specified finished product manufacturer, demonstrated full compliance with the proposed Finished Product Specification.

EXCIPIENTS

All the excipients have been specified as complying with the corresponding Ph Eur monographs. Certificates of Analysis have been provided for all excipients.

IMMEDIATE PACKAGING

The proposed primary packaging consists of 10-ml and 50-ml Type I colourless glass vials sealed with a fluoropolymer-coated grey rubber stoppers and aluminium crimping cap. Compliance with DIN-ISO 8362 dimensions and Ph Eur requirements for Type I glass and rubber stoppers has been confirmed.

CONTROL TESTS ON THE FINISHED PRODUCT

The finished product specification contains appropriate controls for a product of this nature and is satisfactory.

Analytical data reported for full-scale production batches of both fill sizes demonstrated full compliance with the proposed finished product specification.

Analytical Methods
The proposed analytical methods are pharmacopoeial methods and have been validated for their intended use.

STABILITY

Stability data reported for each of the proposed fill sizes support the product shelf-life of 18 months when stored under refrigeration and protected from light..

BIOEQUIVALENCE AND BIOAVAILABILITY

The absence of bioequivalence data is in line with CPMP guidance on bioequivalence exemption for parenteral solutions intended solely for administration by injection.

4. ADMINISTRATIVE DETAILS

MAA FORM

Satisfactory

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Satisfactory.

LABELLING

Satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

Satisfactory.

EXPERT REPORT

Satisfactory

5. PHARMACEUTICAL RECOMMENDATION

Marketing Authorisations may be granted for these products.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

ATC Code: L01B A – Folic acid analogue

2. BACKGROUND

Doxorubicin is one of the most widely used antineoplastic agent in clinical practice. It is often used in association with other antineoplastic agents for various forms of cancer. Cardiotoxicity is the characteristic feature with the potential for development of congestive heart failure with increasing total cumulative doses. Myelosuppression is the other dose limiting toxicity.

3. INDICATIONS

"Antimitotic and cytotoxic. Doxorubicin has been used successfully to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas.
Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent."

4. DOSE & DOSE SCHEDULE

"The solution is given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe cellulitis and vesication.

Dosage is usually calculated on the basis of body surface area. On this basis, 60-75 mg/m^2 may be given every three weeks when doxorubicin is used alone. If it used in combination with other antitumour agents having overlapping toxicity, the dosage of doxirubicin may need to be reduced to 30-40mg/m^2 every three weeks.

If the dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect of mucositis; however, there are still some who believe that dividing the dose over three successive days (0.4 – 0.8mg/kg or 20-25mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three-weekly regimen. The recommended dosage is 20mg/m^2 weekly, although, objective responses have been seen at 16mg/m^2. Weekly administration leads to a reduction in cardiotoxicity.

Dosage may also need to be reduced in children and the elderly.

If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Serum Bilirubin Levels	1.2 – 3.0 mg/100ml	> 3.0 mg/100ml
BSP Retention	9 – 15%	> 15%
Recommended Dose	50% Normal dose	25% Normal dose

5. TOXICOLOGY

No new data has been submitted and none is required.

6. CLINICAL PHARMACOLOGY

The clinical pharmacology of doxorubicin is well known. DNA intercalation leads to inhibition of synthesis of DNA, RNA and proteins, formation of reactive free radicals and superoxides, chelation of divalent cations and the inhibition of NA-K ATPase and the binding of doxorubicin to certain constituents of cell membranes.

After IV administration the plasma disappearance is triphasic with half-lives of 12 minutes, 3.3 hours and 30 hours.

6.1 BIOEQUIVALENCE

Bioequivalence studies were not necessary, as this is a product for intravenous administration.

7. EFFICACY

No new efficacy studies have been submitted and none is required. Doxorubicin has been in clinical use for many years.

8. SAFETY

The safety profile of the product is known. No new data has been submitted and none is required.

9. EXPERT REPORT

The clinical expert report has been written by an independent Consultant Pharmaceutical Physician. The report is brief and repeatedly emphasises that the effects and adverse effects are likely to be similar to the reference product.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory and consistent with that of the reference product.

11. PATIENT INFORMATION LEAFLET

The patient information leaflet is satisfactory.

12. LABELLING

The labelling is satisfactory.

13. DISCUSSION

Doxorubicin is a well known drug and has been used in the treatment of various types of cancer for many years. Its efficacy and safety profile is known.. There is no clinical objection to the grant of a license.

14. CONCLUSIONS

There is no clinical objection to the grant of a marketing authorisation for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Doxorubicin 2mg/ml concentrate for solution for 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

Doxorubicin 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, Doxorubicin Solution for injection 2mg/ml .

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 doxorubicin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471 & PL 04543/0476

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 25/10/2002.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 20/11/2002.
3	Following assessment of the application the MHRA requested further information relating to the dossier on24/01/2003, 24/03/2003, 20/05/2003, 02/03/2004, 06/05/2005 and 22/03/2006.
4	The applicant responded to the MHRA's requests, providing further information on 19/09/2003, 01/02/2005, 03/11/2005, 19/12/2005 and 27/03/2006.
5	The application was determined on 28/06/2006.

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471 & PL 04543/0476

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains doxorubicin hydrochloride 2mg. Each vial contains 50 mg doxorubicin hydrochloride in 25 ml.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
The concentrate is a clear blood-red solution, free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antimitotic and cytotoxic. Doxorubicin has been used successfully to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas.
Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent.

4.2 Posology and method of administration

For intravenous administration.

Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

Dosage is usually calculated on the basis of body surface area. On this basis, 60-75 mg/m^2 may be given every three weeks when doxorubicin is used alone. If it used in combination with other antitumour agents having overlapping toxicity, the dosage of doxorubicin may need to be reduced to 30-40mg/m^2 every three weeks.

If dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect of mucositis; however, there are still some who believe that dividing the dose over three successive days (0.4-0.8mg/kg or 20-25mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity. If dosage is to be calculated on the basis of body weight, 1.2-2.4mg/kg should be given as a single dose every three weeks.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three-weekly regimen. The recommended dosage is 20mg/m^2 weekly, although, objective responses have been seen at 16mg/m^2. Weekly administration leads to a reduction in cardiotoxicity.

Dosage may also need to be reduced in children and the elderly.

If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Serum Bilirubin Levels	1.2 – 3.0 mg/100ml	> 3.0 mg/100ml
BSP Retention	9 - 15%	>15%
Recommended Dose	50% Normal dose	25% Normal Dose

4.3 Contraindications

Dosage should not be repeated in the presence of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised.

4.4 Special warnings and precautions for use

A cumulative dose of 450-500 mg/m2 should only be exceeded with extreme caution. Above this level, the risk of irreversible congestive cardiac failure increases greatly. The total dose of doxorubicin administered to the individual

patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as high-dose i.v. cyclophosphamide, mediastinal irradiation or related anthracycline compounds such as daunorubicin.
Administration weekly has been shown to be associated with reduced cardiotoxicity compared with a three weekly schedule, allowing patients to be treated with a higher cumulative dose.
It should be noted that cardiac failure may also occur several weeks after administration and may not respond to treatment. Baseline and follow-up ECGs during and immediately after drug administration are advisable. Transient ECG changes, such as T-wave flattening, S-T segment depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A reduction of the QRS wave is considered more indicative of cardiac toxicity. If this change occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

4.5 Interaction with other medicinal products and other forms of interaction

High dose ciclosporin increases the serum levels and myelotoxicity of doxorubicin.

4.6 Pregnancy and lactation

There is no conclusive evidence as to whether doxorubicin may adversely affect human fertility or cause teratogenesis. Experimental data however suggest that doxorubicin may harm the foetus and should not therefore be administered to pregnant women or those who are breast feeding.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septcaemia, septic shock, haemorrhages, tissue hypoxia or death.

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

Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly, without premonitory ECG changes.

Doxorubicin solution for injection may impart a red colour to the urine particularly to the first specimen passed after the injection, and patients should be advised that there is no cause for alarm.

Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped. Nausea, vomiting and diarrhoea may also occur.

The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation signifies a small degree of extravasation and the infusion should be stopped and restarted in another vein.

Other side effects include mucositis, skin rashes, fever, hyperuricaemia, amenorrhoea, anaphylaxis, bronchospam and dyspnoea.

4.9 Overdose

Single doses of 250mg and 500mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression, the effects of which are greatest between 10 and 15 days after administration. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxorubicin is an antitumour agent. Although the exact mechanism of action is not yet known, the tumour cells are probably killed through drug-induced alterations of nucleic acid synthesis.
The proposed mechanism of action include the following:

DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of

divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrum and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.

5.2 Pharmacokinetic properties

After i.v administration, the plasma disappearance curve of doxorubicin is triphasic with half- lives of 12 minutes, 3.3 hours and 33 hours. The relatively long terminal elimination half-life reflects doxorubicin's distribution into deep tissue compartment. Only about 33 to 50% of fluorescent or tritiated drug (or degradation products), respectively, can be accounted for in urine, bile and faeces for upto 5 days after i.v administration. The remainder of the doxorubicin and degradation products appear to be retained for long periods of time in body tissues.

In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalysed by cytoplasmic nadph depenedent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Microsomal glycosidases present in most tissues split doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjunction to sulphate or glucuronide esters, and excretion in bile.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium chloride
Water for injections

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs.

6.3 Shelf life

Unopened: 18 months

After dilution (for solutions diluted to a concentration of 1.0mg/ml or 0.1mg/ml):

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

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

6.4 Special precautions for storage

Store at 2 - 8 °C. Keep the container in the outer carton.
After reconstitution: See section 6.3 for complete storage instructions.
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

6.5 Nature and contents of container

Type I clear glass vials with grey teflon-coated chlorobutyl rubber stopper and aluminium crimp cap, packed in a carton.
Package sizes:
Packs of one vial containing 50mg/25ml of doxorubicin hydrochloride.

6.6 Special precautions for disposal

Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

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 doxorubicin injection should 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

For single dose use only. Discard any unused solution immediately after initial use.

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

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.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably soaking overnight and then water. All cleaning materials should be disposed of as indicated previously.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0471

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/06/2006

10 DATE OF REVISION OF THE TEXT

28/06/2006

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0476

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Doxorubicin Hydrochloride 2mg. Each vial contains 10 mg Doxorubicin Hydrochloride in 5 ml.
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
The concentrate is a clear blood-red solution, free from particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antimitotic and cytotoxic. Doxorubicin has been used successfully to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas.
Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent.

4.2 Posology and method of administration

For intravenous administration.
Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

Dosage is usually calculated on the basis of body surface area. On this basis, 60-75 mg/m^2 may be given every three weeks when doxorubicin is used alone. If it used in combination with other antitumour agents having overlapping toxicity, the dosage of doxorubicin may need to be reduced to 30-40mg/m^2 every three weeks.

If dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect of mucositis; however, there are still some who believe that dividing the dose over three successive days (0.4-0.8mg/kg or 20-25mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity. If dosage is to be calculated on the basis of body weight, 1.2-2.4mg/kg should be given as a single dose every three weeks.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three-weekly regimen. The recommended dosage is 20mg/m^2 weekly, although, objective responses have been seen at 16mg/m^2. Weekly administration leads to a reduction in cardiotoxicity.

Dosage may also need to be reduced in children and the elderly.

If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Serum Bilirubin Levels	1.2 – 3.0 mg/100ml	> 3.0 mg/100ml
BSP Retention	9 - 15%	>15%
Recommended Dose	50% Normal dose	25% Normal Dose

4.3 Contraindications

Dosage should not be repeated in the presence of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised.

4.4 Special warnings and precautions for use

A cumulative dose of 450-500 mg/m^2 should only be exceeded with extreme caution. Above this level, the risk of irreversible congestive cardiac failure increases greatly. The total dose of doxorubicin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as high-dose i.v. cyclophosphamide, mediastinal irradiation or related anthracycline compounds such as daunorubicin.

Administration weekly has been shown to be associated with reduced cardiotoxicity compared with a three-weekly schedule, allowing patients to be treated with a higher cumulative dose.

It should be noted that cardiac failure may also occur several weeks after administration and may not respond to treatment. Baseline and follow-up ECGs during and immediately after drug administration are advisable. Transient ECG changes, such as T-wave flattening, S-T segment depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A reduction of the QRS wave is considered more indicative of cardiac toxicity. If this change occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

4.5 Interaction with other medicinal products and other forms of interaction

High dose ciclosporin increases the serum levels and myelotoxicity of doxorubicin.

4.6 Pregnancy and lactation

There is no conclusive evidence as to whether doxorubicin may adversely affect human fertility or cause teratogenesis. Experimental data however suggest that doxorubicin may harm the foetus and should not therefore be administered to pregnant women or those who are breast feeding.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death.

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA damaging anti-neoplastic agents. Such cases could have a short (one to three year) latency period.
Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly, without premonitory ECG changes.
Doxorubicin solution for injection may impart a red colour to the urine particularly to the first specimen passed after the injection, and patients should be advised that there is no cause for alarm.
Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped. Nausea, vomiting and diarrhoea may also occur.
The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation signifies a small degree of extravasation and the infusion should be stopped and restarted in another vein.
Other side effects include mucositis, skin rashes, fever, hyperuricaemia, amenorrhoea, anaphylaxis, bronchospasm and dyspnoea.

4.9 Overdose

Single doses of 250mg and 500mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression, the effects of which are greatest between 10 and 15 days after administration. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing.
Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxorubicin is an antitumour agent. Although the exact mechanism of action is not yet known, the tumour cells are probably killed through drug-induced alterations of nucleic synthesis.

The proposed mechanisms of action include the following:

DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to

certain constituents of cell membranes (particularly to the membrane lipids, spectrum and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bonemarrow. Doxorubicin does not cross the blood-brain barrier.

5.2 Pharmacokinetic properties

After i.v. administration, the plasma disappearance curve of doxorubicin is triphasic with half-lives of 12 minutes, 3.3 hours and 30 hours. The reletively long terminal elimination half-life reflects doxorubicin's distribution into deep tissue compartment. Only about 33 to 50% of fluorescent or tritiated drug (or degradation products), respectively, can be accounted for in urine, bile and faeces for up to 5 days after i.v administration. The remainder of the doxorubicin and degradation products appear to be retained for long periods of time in body tissues.

In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalysed by cytoplasmic nadph dependent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Microsomal glycosidases present in most tissues split doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjuction to sulphate or glucuronide esters, and excretion in bile.

5.3 Preclinical safety data

There are no pre-clinical data available which are additional to those included in other sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium chloride
Water for injections

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs.

6.3 Shelf life

Unopened: 18 months

After dilution (for solutions diluted to a concentration of 1.0mg/ml or 0.1mg/ml):

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

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

6.4 Special precautions for storage

Store at 2 - 8 °C. Keep the container in the outer carton.
After reconstitution: See section 6.3 for complete storage instructions.
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

6.4 Nature and contents of container

Type I clear glass vials with grey teflon-coated chlorobutyl rubber stopper and aluminium crimp cap, packed in a carton.

Package sizes:

Packs of one vial containing 10mg/5ml of doxorubicin hydrochloride.

6.5 Special precautions for disposal

Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

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 doxorubicin injection should should wear protective clothing: goggles, gownsand disposable gloves and masks
- All items used for administration or cleaning, including gloves, should be placed in highrisk, waste-disposal bags for high temperature incineration

For single dose use only. Discard any unused solution immediately after initial use.

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

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.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably soaking overnight and then water. All cleaning materials should be disposed of as indicated previously.

7 MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04543/0476

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/06/2006

10 DATE OF REVISION OF THE TEXT

28/06/2006

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471 & PL 04543/0476

PATIENT INFORMATION LEAFLET & TECHNICAL LEAFLET

PACKAGE LEAFLET

Doxorubicin 2mg/ml Concentrate for Solution for Infusion
Doxorubicin 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, nurse or pharmacist.

In this leaflet:

The active substance in the injection is doxorubicin hydrochloride.

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

Doxorubicin 2mg/ml Concentrate for Solution for Infusion is manufactured by EBEWE Pharma Ges.m.b.H. Nfg. KG, A-4866 Unterach, Mondseestrasse 11, Austria for the Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham LL13 9UF, United Kingdom.

1. WHAT IS DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION AND WHAT IS IT USED FOR?

The concentrate for solution for infusion is a clear, blood red solution, free of particles. The sterile solution is supplied in clear glass vials with rubber stoppers. Each vial contains either 10 mg or 50 mg of the active ingredient, doxorubicin hydrochloride, in 5 ml or 25 ml, respectively.

Doxorubicin belongs to a group of medicines known as cytotoxics, which are used in the treatment of cancer. Doxorubicin may be used to treat leukaemia, lymphomas, sarcomas, cancer in children and tumours (particularly in the breast and lung).

2. BEFORE YOU ARE GIVEN DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

You should not be given doxorubicin:

- if you are allergic to doxorubicin or any of the other ingredients
- if you have problems with your bone marrow
- if you have mouth ulcers or a sensation of burning in the mouth after an earlier course of doxorubicin

Your doctor will take special care when giving you doxorubicin:

- if you have recently had treatment with other cytotoxic drugs or you are having radiotherapy
- if you have heart problems

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

Your doctor will check your blood before, during and after every treatment cycle and will monitor your heart by giving you an ECG test. If the results of any of these tests are abnormal, treatment will only be resumed when all readings are back to normal.

Pregnancy

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

Female patients should also avoid getting pregnant while being treated with doxorubicin and for at least six months afterwards. Male patients receiving doxorubicin 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 doxorubicin treatment is started.

Breast-feeding

Doxorubicin should not be given to you if you are breast-feeding, because doxorubicin may pass into breast milk and may affect the baby.

Driving and using machines:

If you are experiencing side-effects which could affect your ability to drive, you should avoid driving or operating machinery until these have worn off.

Being given doxorubicin at the same time as other medication

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. Ciclosporin is an example of a medicine which could affect doxorubicin.

Doxorubicin 2mg/ml Concentrate for Solution for Infusion contains 0.76mmol of sodium in a 5ml vial and 3.84mmol of sodium in a 25ml vial. The amount of sodium will need to be taken into consideration by patients on a controlled sodium diet

3. HOW DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION WILL BE GIVEN TO YOU

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

Doxorubicin 2mg/ml Concentrate for Solution for Infusion will be administered by intravenous infusion after dilution according to directions.

The usual dose of doxorubicin in adults is 60 to 75 mg per square metre of body surface area every three weeks. If doxorubicin is given in combination with other cytotoxic drugs then the dosage will be reduced to 30 to 40 mg per square metre of body surface area every three weeks.

Alternatively, you may be given smaller doses of 20 to 25mg per square metre of body surface area every day for three days at three week intervals, or 20mg per square metre of body surface area once a week.

The total dose you are given should not usually be more than 450-500 mg per square metre of body surface area.

Dosage will be reduced in children and the elderly or in patients with liver problems.

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

4. POSSIBLE SIDE EFFECTS

The most common unwanted effects are nausea, vomiting and diarrhoea. Hair loss is common and men with beards will notice that their beards stop growing. All hair growth will return to normal after finishing the course of doxorubicin treatment.

You may notice that your urine is red, particularly when treatment is first started. Do not worry about this as it will soon return to its normal colour.

Less commonly, doxorubicin causes heart problems, with rapid heart rate, heart failure, breathlessness, ankle swelling, inflammation of mucous membranes, skin rashes, fever, blood disorders, severe breathing problems, hyperuricaemia (excessive amounts of uric acid in the blood) and allergic reactions. Women may find that their periods stop temporarily. Some patients have had bone marrow problems, causing mouth ulcers, sore throat or a tendency to bruise or bleed easily, fever, infections, blood disorders (including infections of the blood), skin problems and death. In rare cases, when used in combination with other cytotoxic drugs, doxorubicin has been known to cause leukaemia.

You may notice stinging, burning, redness or swelling around the injection site. You should let the person giving you the injection know **immediately** if this happens.

Doxorubicin may harm unborn babies or cause miscarriage (see section on pregnancy) and may also affect fertility in men and women.

During the treatment with doxorubicin your general condition will be closely monitored.

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

5. STORING DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Keep out of the reach and sight of children
Store at 2 - 8 °C. Keep the container in the outer carton.
Do not use after the expiry date stated on the label or if there any signs of deterioration such as discolouration.
For single dose use only. Discard any unused solution immediately after initial use.
When diluted according to directions, product should be stored at 2-8°C for 24 hours

This leaflet was prepared in .....

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SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. Trade Name of the Medicinal Product

Doxorubicin 2mg/ml Concentrate for Solution for Infusion

2. Qualitative and Quantitative Composition

Each ml contains doxorubicin hydrochloride 2 mg.
Each vial contains 10mg doxorubicin hydrochloride in 5ml or 50mg doxorubicin hydrochloride in 25ml

For excipients, see 6.1

3. Pharmaceutical Form

Concentrate for solution for infusion

The concentrate is a clear blood-red solution, free from particles.

Clinical Particulars

4.1. Therapeutic Indications

Antimitotic and cytotoxic. Doxorubicin has been used successfully to produce regression in a wide range of neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular breast and lung carcinomas.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs. Doxorubicin cannot be used as an antibacterial agent.

4.2. Posology and Method of Administration

For intravenous administration.

Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended
in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

Dosage is usually calculated on the basis of body surface area. On this basis, 60-75 mg/m^2 may be given every three weeks when doxorubicin is used alone. If it used in combination with other antitumour agents having overlapping toxicity, the dosage of doxorubicin may need to be reduced to 30-40mg/m^2 every three weeks.

If dosage is calculated on the basis of body weight, it has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect of mucositis; however, there are still some who believe that dividing the dose over three successive days (0.4-0.8mg/kg or 20-25mg/m^2 on each day) gives greater effectiveness though at the cost of higher toxicity. If dosage is to be calculated on the basis of body weight, 1.2-2.4mg/kg should be given as a single dose every three weeks.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three-weekly regimen. The recommended dosage is 20mg/m^2 weekly, although, objective responses have been seen at 16mg/m^2. Weekly administration leads to a reduction in cardiotoxicity.

Dosage may also need to be reduced in children and the elderly.

If hepatic function is impaired, doxorubicin dosage should be reduced according to the following table:

Serum Bilirubin Levels	1.2 – 3.0 mg/100ml	> 3.0 mg/100ml
BSP Retention	9 - 15%	>15%
Recommended Dose	50% Normal dose	25% Normal Dose

4.3. Contra-indications

Dosage should not be repeated in the presence of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised.

4.4. Special Warnings and Precautions for Use

A cumulative dose of 450-500 mg/m^2 should only be exceeded with extreme caution. Above this level, the risk of irreversible congestive cardiac failure increases greatly. The total dose of doxorubicin administered to the individual patient should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents such as high-dose i.v. cyclophosphamide, mediastinal irradiation or related anthracycline compounds such as daunorubicin.

Administration weekly has been shown to be associated with reduced cardiotoxicity compared with a three-weekly schedule, allowing patients to be treated with a higher cumulative dose.

It should be noted that cardiac failure may also occur several weeks after administration and may not respond to treatment. Baseline and follow-up ECGs during and immediately after drug administration are advisable. Transient ECG changes, such as T-wave flattening, S-T segment depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A reduction of the QRS wave is considered more indicative of cardiac toxicity. If this change occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

4.5. Interactions with other Medicaments and other forms of Interaction

High dose ciclosporin increases the serum levels and myelotoxicity of doxorubicin.

4.6. Pregnancy and Lactation

There is no conclusive evidence as to whether doxorubicin may adversely affect human fertility or cause teratogenesis. Experimental data however suggest that doxorubicin may harm the foetus and should not therefore be administered to pregnant women or those who are breast feeding.

4.7. Effects on Ability to Drive and Use Machines

None stated

4.8. Undesirable Effects

Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death.

The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA damaging anti-neoplastic agents. Such cases could have a short (one to three year) latency period.

Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly, without premonitory ECG changes.

Doxorubicin solution for injection may impart a red colour to the urine particularly to the first specimen passed after the injection, and patients should be advised that there is no cause for alarm.

Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped. Nausea, vomiting and diarrhoea may also occur.

The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation signifies a small degree of extravasation and the infusion should be stopped and restarted in another vein.

Other side effects include mucositis, skin rashes, fever, hyperuricaemia, amenorrhoea, anaphylaxis, bronchospasm and dyspnoea.

4.9. Overdose

Single doses of 250mg and 500mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours and severe myelosuppression, the effects of which are greatest between 10 and 15 days after administration. Treatment should aim to support the patient during this period and should utilise such measures as blood transfusions and reverse barrier nursing.

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines

Pharmacological Properties

5.1. Pharmacodynamic Properties

Doxorubicin is an antitumour agent. Although the exact mechanism of action is not yet known, the tumour cells are probably killed through drug-induced alterations of nucleic acid synthesis.

The proposed mechanisms of action include the following:

DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrum and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.

5.2. Pharmacokinetic Properties

After i.v. administration, the plasma disappearance curve of doxorubicin is triphasic with half-lives of 12 minutes, 3.3 hours and 30 hours. The relatively long terminal elimination half-life reflects doxorubicin's distribution into deep tissue compartment. Only about 33 to 50% of fluorescent or tritiated drug (or degradation products), respectively, can be accounted for in urine, bile and faeces for up to five days after i.v. administration. The remainder of the doxorubicin and degradation products appear to be retained for long periods of time in body tissues.

In cancer patients, doxorubicin is reduced to adriamycinol, which is an active cytotoxic agent. This reduction appears to be catalysed by cytoplasmic NADPH dependent aldo-keto reductases that are found in all tissues and play an important role in determining the overall pharmacokinetics of doxorubicin.

Microsomal glycosidases present in most tissues spilt doxorubicin and adriamycinol into inactive aglycones. The aglycones may then undergo 0-demethylation, followed by conjunction to sulphate or glucuronide esters, and exctretion in bile.

5.3. Preclinical Safety Data

There are no preclinical data available which are additional to those in other sections of this SPC.

Pharmaceutical Particulars

6.1. List of Excipients

Hydrochloric acid
Sodium chloride
Water for injections

6.2. Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that doxorubicin be mixed with other drugs.

6.3 Shelf life

Unopened: 18 months

After dilution (for solutions diluted to a concentration of 1.0mg/ml or 0.1mg/ml):

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

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

6.4 Special precautions for storage

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

After reconstitution: See section 6.3 for complete storage instructions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C.

6.5. Nature and Contents of Container

Type I clear glass vials with grey teflon-coated chlorobutyl rubber stopper and aluminium crimp cap, packed in a carton.

Package sizes:

Packs of one vial containing 10mg/5ml of doxorubicin hydrochloride.

Packs of one vial containing 50mg/25ml of doxorubicin hydrochloride.

6.6. Instruction for Use/Handling

Doxorubicin 2mg/ml Injection should be diluted to a concentration of either 1.0mg/ml or 0.1mg/ml (please refer to Section 6.3 for the recommended in-use shelf life).

Commonly used acceptable infusion solutions are sodium chloride injection, dextrose injection 5% or sodium chloride and dextrose injection.

The solution is made up before being given via the tubing of a freely running intravenous infusion, taking two to three minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

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 doxorubicin injection should should wear protective clothing: goggles, gownsand 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

For single dose use only. Discard any unused solution immediately after initial use.

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

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.

Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably soaking overnight and then water. All cleaning materials should be disposed of as indicated previously.

Administrative Data

7. Marketing Authorisation Holder

CP Pharmaceuticals Ltd
Ash Road North
Wrexham LL13 9UF
United Kingdom

7. Marketing Authorisation Number

Doxorubicin 2mg/ml Injection BP (10mg/5ml) - PL 04543/0476
Doxorubicin 2mg/ml Injection BP (50mg/25ml) - PL 04543/0471

9. Date of First Authorisation/Renewal of Authorisation

10. Date of (Partial) Revision of the Text

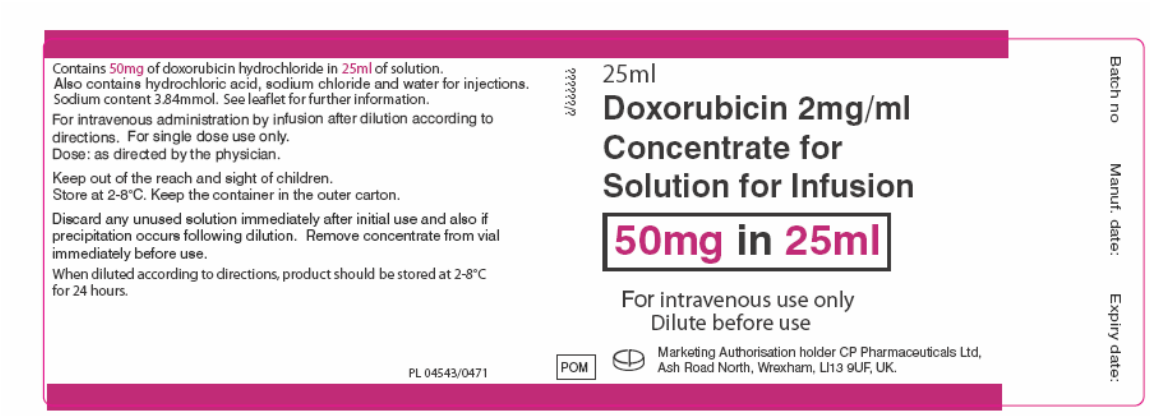
DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0471

LABELLING

CARTON

LABEL

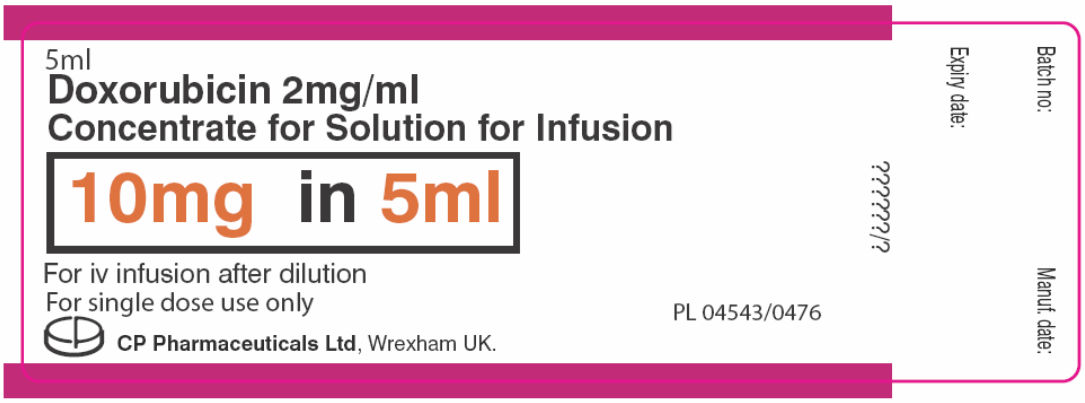

Contains 50mg of doxorubicin hydrochloride in 25ml of solution.
Also contains hydrochloric acid, sodium chloride and water for injections.
Sodium content 3.84mmol. See leaflet for further information.
For intravenous administration by infusion after dilution according to directions. For single dose use only.
Dose: as directed by the physician.
Keep out of the reach and sight of children.
Store at 2-8°C. Keep the container in the outer carton.
Discard any unused solution immediately after initial use and also if precipitation occurs following dilution. Remove concentrate from vial immediately before use.
When diluted according to directions, product should be stored at 2-8°C for 24 hours.
PL 04543/0471
25ml
Doxorubicin 2mg/ml Concentrate for Solution for Infusion
50mg in 25ml
For intravenous use only
Dilute before use
POM
Marketing Authorisation holder CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LI13 9UF, UK.
Batch no
Manuf. date:
Expiry date:

DOXORUBICIN 2MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION (DOXORUBICIN HYDROCHLORIDE)

PL 04543/0476

CARTON

LABEL


5ml
Doxorubicin 2mg/ml
Concentrate for Solution for Infusion
10mg in 5ml
For iv infusion after dilution
For single dose use only
CP Pharmaceuticals Ltd, Wrexham UK.
PL 04543/0476
Batch no:
Expiry date:
Manuf. date: