

Public Assessment Report

**DOXORUBICIN HYDROCHLORIDE 2MG/ML SOLUTION
FOR INFUSION**

PL 22472/0003

Applicant: medac Gesellschaft für klinische Spezialpräparate mbH

**DOXORUBICIN HYDROCHLORIDE 2MG/ML SOLUTION FOR
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LAY SUMMARY

The MHRA has granted medac Gesellschaft für klinische Spezialpräparate mbH a Marketing Authorisation (licence) for the medicinal product Doxorubicin Hydrochloride 2mg/ml Solution for Infusion (PL 22472/0003) on 1st April 2008. Doxorubicin Hydrochloride 2mg/ml Solution for Infusion is a prescription-only medicine (POM) that contains doxorubicin hydrochloride.

Doxorubicin is one of a group of medicines known as anthracyclines. It works by killing tumours and blood cancer cells.

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

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Doxorubicin Hydrochloride 2mg/ml Solution for Infusion (PL 22472/0003) to medac Gesellschaft für klinische Spezialpräparate mbH on 1st April 2008. The product is available as a prescription-only medicine (POM).

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product to Adriblastina R.T.U., 2 mg/ml, solution for injection (originally granted to Pharmacia in October 1989).

The product contains the active ingredient doxorubicin hydrochloride and is indicated in a wide range of neoplastic conditions, including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours, in particular of breast and lung. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma in situ and papillary tumours of the bladder, by intravesical administration.

Doxorubicin is an anthracycline antibiotic. It exerts its antineoplastic effect via cytotoxic mechanisms of action. Doxorubicin has demonstrated activity in various carcinomas, and is also frequently used in combination chemotherapy regimens with other cytostatic drugs.

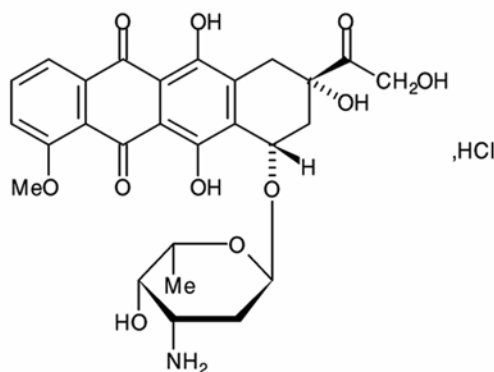
PHARMACEUTICAL ASSESSMENT

Active substance

INN: Doxorubicin hydrochloride

Chemical Name: (8S,10S)-10-[(3-Amino-2,3,6-trideoxy- α -L-lyxo hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-Tetrahydrotetracene-5,12-dione hydrochloride

Structure:



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

Molecular Weight: 580.00

Doxorubicin hydrochloride is an orange-red crystalline powder and practically odourless. It has a melting point of 185°C.

The manufacture and control of the active substance doxorubicin hydrochloride is covered by European Pharmacopoeia Certificates of Suitability.

A suitable retest period has been proposed by the active substance manufacturer, based on appropriate stability data.

Other Ingredients

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

None of the excipients are sourced from animal products.

Pharmaceutical Development

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

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

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

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

Container-Closure System

The commercial packaging consists of Type I colourless glass vials with film-coated chlorobutyl/butyl stoppers and flip-off aluminium seals. Pack sizes are 5, 10, 25, 75 and 100ml.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. The glass vial and rubber stopper have been shown to comply with current guidelines concerning the use of materials in contact with injectable products.

Stability of the product

Stability data have been provided, in compliance with ICH guidelines, for solution produced by the finished product manufacturer in the packaging proposed for marketing. These data support a shelf-life of 2 years (which reduces to 48 hours after reconstitution), with the storage conditions 'Keep container in the outer carton', 'Protect from light' and 'Store in a refrigerator (2-8°C)'.

The applicant has committed to performing follow-up stability studies in accordance with the submitted stability protocol.

Bioequivalence/bioavailability

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

Summary of Product Characteristics (SPC)

The SPC is pharmaceutically acceptable.

Patient Information Leaflet (PIL)

The PIL is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Labels

The labels are pharmaceutically satisfactory.

CONCLUSION

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

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance.

PRECLINICAL ASSESSMENT

This application is a generic product of Adriblastina R.T.U., 2 mg/ml, solution for injection (Pharmacia), which have been licensed within the EU for over 10 years.

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

CLINICAL ASSESSMENT

1. INDICATIONS

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

2. DOSE & DOSE SCHEDULE

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

3. CLINICAL PHARMACOLOGY

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

4. EFFICACY

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

5. SAFETY

The clinical expert report provides an adequate review of the clinical safety of doxorubicin hydrochloride. No reference is made to any new data that would have affected the marketing authorisation for the product under consideration.

6. EXPERT REPORTS

The expert reports are written by appropriately qualified persons.

7. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is consistent with the reference product and is satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)

This is consistent with the reference product and is satisfactory. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

9. LABELLING

Full colour mock-ups are provided and are satisfactory.

10. MEDICAL CONCLUSION

A marketing authorisation may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Doxorubicin Hydrochloride 2mg/ml 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 an application of this type.

EFFICACY

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

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with doxorubicin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 30 th November 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 st December 2005
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 17 th July 2006 and 21 st February 2008, and quality dossier on 6 th April 2006, 26 th January 2007, 15 th February 2008 and 21 st February 2008
4	The applicant responded to the MHRA's requests, providing further information for the clinical dossier on 9 th August 2007 and 3 rd March 2008, and quality dossier on 21 st October 2006, 27 th December 2007, 3 rd March 2008 and 6 th March 2008
5	The applications were determined on 1 st April 2008

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Doxorubicin Hydrochloride 2 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 2 mg Doxorubicin hydrochloride.

Each 5ml vial contains a total content of Doxorubicin hydrochloride of 10 mg.

Each 10ml vial contains a total content of Doxorubicin hydrochloride of 20 mg.

Each 25ml vial contains a total content of Doxorubicin hydrochloride of 50 mg.

Each 75ml vial contains a total content of Doxorubicin hydrochloride of 150 mg.

Each 100ml vial contains a total content of Doxorubicin hydrochloride of 200 mg.

The product contains sodium chloride (3.5 mg sodium per 1 ml). For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The product is a clear, red solution which is practically free of particles.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Antimitotic and cytotoxic. Doxorubicin has been used with success 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 of breast and lung. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma in situ and papillary tumours of the bladder, by intravesical administration.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic drugs.

4.2 Posology and method of administration**1 For intravenous use**

The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 0.9 % or dextrose 5 % into a large vein using a Butterfly needle, taking 2 to 3 minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe local cellulitis and necrosis.

Dosage is usually calculated on the basis of body surface area. On this basis, a dose of 60 - 75 mg/m² body surface area is recommended every three weeks when doxorubicin is used alone. If using the body weight to calculate the dose, dosages of 1.2 – 2.4 mg/kg are recommended. If it is used in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin should be reduced to 30 - 40 mg/m² every three weeks.

Dividing the dose over three successive days (20 - 25mg/m² or 0.4 - 0.8mg/kg on each day) gives greater effectiveness at the cost of higher toxicity. Administration of doxorubicin in a weekly regimen has been shown to be as effective as the 3-weekly regimen. The recommended dosage is 20 mg/m² weekly, although objective responses have been seen at 6 – 12 mg/m². Weekly administration has been shown to be associated with reduced cardiotoxicity compared with a 3-weekly schedule.

Patients who have received prior radiotherapy to the mediastinal/pericardial area should not receive doxorubicin greater than a total cumulative dose of 400 mg/m².

Dosage may also need to be reduced in young children and the elderly. It is recommended that the total cumulative dose of doxorubicin for adults aged 70 or older be restricted to 450 mg/m² body surface area.

2 For intravesical use

Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma after transurethral resection. However, this method is contraindicated in invasive bladder tumours.

The patient should not drink fluids for 12 hours prior to the treatment.

25 ml of the solution, containing 50 mg of doxorubicin hydrochloride, is mixed under sterile conditions with 20 ml normal saline and instilled via catheter into the bladder.

After removal of the catheter, the patient stays lying on his back for 15 minutes.

At 15-minute intervals, the patient makes a quarter turn over a period of 1 hour. At the end of this period, the patient may void.

This procedure can be repeated at monthly intervals.

3 Impaired hepatic function

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

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

4.3 Contraindications

Hypersensitivity to the active substance doxorubicin hydrochloride or to any of the excipients. Doxorubicin Hydrochloride is contra-indicated in patients with pre-existing myelosuppression (e.g. induced by previous antitumour treatment).

Dosage should not be repeated in the presence or development 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.

Doxorubicin Hydrochloride is contraindicated in patients with impaired cardiac function and in patients who have been treated previously with complete cumulative doses of anthracyclines (see section 4.4, Special warnings and precautions for use). In patients who have received anthracyclines previously, addition of further anthracycline therapy can be contemplated only after careful assessment of the cardiac status of the patient. The potential benefit of additional anthracycline therapy must carefully be weighed against the possible risks of cardiotoxicity.

Doxorubicin Hydrochloride is further contraindicated in patients with increased haemorrhagic tendency, stomatitis, generalised infections, markedly impaired liver function and cystitis (in the case of intravesical application).

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, but this condition could even occur with doses of 240 mg/m². These effects may occur during infusion, but also several weeks after termination of therapy.

Cardiac failure may not respond to treatment. Early clinical diagnosis of drug-induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. Base line ECG and periodic follow up ECG during and immediately after active drug therapy is an advisable precaution. Transient ECG changes, such as T-wave flattening, S-T depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Precaution is also required during simultaneous or previous radiotherapy of the mediastinal/pericardial area or after treatment with other cardiotoxic substances.

Doxorubicin must not be given intrathecally or intramuscularly or by long-term infusion. Direct intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates the tissues. If a central vein catheter is used then infusion of doxorubicin in sodium chloride 0.9% injection is advised.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.

On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation. Even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein. In the event of inadvertent extravasation, ice packs should be applied to the injection site. Local injection of dexamethasone or hydrocortisone may be used to minimise local tissue necrosis. Hydrocortisone cream 1% may also be applied locally.

Careful haematological monitoring is required due to the myelosuppressive effects. Pre-treatment with digoxin (250 µg daily starting 7 days before doxorubicin) showed a protective effect against cardiotoxicity. In cases of hyperuricaemia, an application of xanthinoxidase-blocking drugs may be indicated.

Like all chemotherapy, therapy with doxorubicin hydrochloride should be carried out only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

This medicinal product contains 3.5 mg sodium per 1 ml of doxorubicin hydrochloride solution for infusion. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of other antineoplastic agents, e.g.: anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C and taxanes can potentiate the risk of doxorubicin-induced congestive heart failure. The disposition of doxorubicin was found to be significantly altered when it was administered immediately after a short intravenous infusion of paclitaxel. The co-administration of paclitaxel causes a decreased clearance of doxorubicin and more neutropenic and stomatitis episodes have been observed.

Increased cardiotoxicity has also been reported after simultaneous intake of cardioactive drugs, e.g., calcium channel blockers and verapamil (with an increase of doxorubicin peak levels, terminal-half life and volume of distribution). The bioavailability of digoxin decreases during doxorubicin therapy. Careful monitoring of the heart function is required in all such concomitant therapeutic regimens.

Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects, especially in cardiotoxicity. Drugs inducing cytochrome P-450 (e.g. rifampicin, barbiturates including phenobarbital) may increase the metabolism of doxorubicin, possibly decreasing the efficacy of doxorubicin.

If doxorubicin therapy is followed by administration of cyclophosphamide, an increased rate of haemorrhagic cystitis has been reported.

The absorption of antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate) is decreased after concomitant use of doxorubicin.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Co-administration of heparin and doxorubicin can lead to an increase in the rate of doxorubicin clearance. Furthermore, precipitates may form and lead to a loss of efficacy of both drugs (see section 6.2, Incompatibilities).

Disturbed haemotopoiesis has been observed after co-administration of substances influencing the bone-marrow function (e.g. amidopyrine derivatives, antiretroviral drugs, chloramphenicol, phenytoin, sulphonamides). Increased neutropenia and thrombocytopenia have been reported after simultaneous use of progesterone. Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

Live vaccines must not be used during doxorubicin therapy due to the risk of generalised disease, which may be lethal. The risk is increased in patients who are immunodepressed due to the underlying disease.

4.6 Pregnancy and lactation

Pregnancy

Doxorubicin has been found in foetal tissue (liver, kidney, lungs) at concentrations several times those in maternal plasma indicating that it does pass the placenta. Doxorubicin proved to be highly teratogenic in rats and mutagenic in the Ames test. Pregnancy is therefore a contraindication for Doxorubicin Hydrochloride.

For safety reasons, men wanting a baby should preserve unexposed sperm prior to treatment with doxorubicin and abstain from engendering a child during and 6 months after therapy. Women with childbearing potential should avoid pregnancy during doxorubicin therapy and 6 months thereafter.

Lactation

The drug has been shown to concentrate in human milk. Because of the potential for serious adverse reactions in nursing infants a decision should be made whether to discontinue breast-feeding or the drug, taking into account the importance of the drug for the woman.

4.7 Effects on ability to drive and use machines

Drowsiness may occur.

4.8 Undesirable effects

1 General

Bone Marrow Depression (myelosuppression): There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 – 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone infiltration by tumour, impaired liver function (when appropriate dosage reduction has not been adopted) and simultaneous treatment with other myelosuppressive agents. Haematological toxicity may require dose reduction or suspension or delay of doxorubicin therapy. Persistent severe myelosuppression may result in superinfection or haemorrhage.

Immunosuppression: Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection.

Enhanced toxicity: It has been reported that doxorubicin may enhance the severity of the toxicity of other anticancer therapies, such as cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy, hepatotoxicity of 6-mercaptopurine and the toxicity of streptozocin or methotrexate (see section 4.5, Interactions).

Infertility: Doxorubicin may cause infertility during the time of drug administration. Although ovulation and menstruation appear to return after termination of therapy, there is only scarce information about the restoration of male fertility.

Hepatic impairment: Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase, bilirubin and BSP. If required, dosage schedules should be reduced accordingly (see section 4.2, Posology and method of administration).

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 (1 - 3 year) latency period.

2 Adverse reactions

2.1 More frequent reactions

Cardiovascular: Cardiotoxicity, i.e., cardiomyopathy, congestive heart failure, supraventricular tachycardia. 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.

Vascular system: Phlebosclerosis.

Dermatological: Extravasation, skin necrosis, cellulitis, vesication, phlebitis, erythematous streaking along the vein proximal to the site of injection. Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped.

The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above (see section 4.2, Posology and method of administration).

Gastrointestinal: Nausea and vomiting, mucositis (stomatitis and oesophagitis), diarrhoea, anorexia, ulceration and necrosis of the colon. Mucositis is a frequent and painful complication of doxorubicin treatment. It most commonly develops 5 to 10 days after treatment, and typically begins as a burning sensation in the mouth and pharynx. It may involve the vagina, rectum and oesophagus, and progress to ulceration with risk of secondary infection and usually subsides in 10 days. Retrospective comparison of the incidence of mucositis suggests that it is less frequent as the intervals between doses increase. Mucositis may be severe in patients who have had previous irradiation to the mucosae.

General: Dehydration, facial flushing (if an injection has been given too rapidly). Doxorubicin 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.

2.2 Less frequent reactions

Dermatological: Urticarial rash, onycholysis, hyperpigmentation of nail beds and dermal increases (primarily in children in a few cases), recall of skin reaction due to prior radiotherapy.

Allergy: Fever, chills, urticaria, anaphylaxis.

Nervous System: Drowsiness.

Ocular: Conjunctivitis, lacrimation.

Renal: Renal damage.

4.9 Overdose

The symptoms of overdosage are likely to be an extension of doxorubicin's pharmacological action. Single doses of 250 mg and 500 mg of doxorubicin have proven to be fatal. Such doses may cause acute myocardial degeneration within 24 hours, and severe myelosuppression, the greatest effects of which are seen between 10 and 15 days after administration. Delayed cardiac failure may occur up to six months after the overdose. Treatment should aim to support the patient during this period. Particular attention should be given to prevention and treatment of possible severe haemorrhage or infections secondary to severe, persistent bone marrow depression. Blood transfusion and reverse barrier nursing may be considered. Hemoperfusion immediately after the overdose proved to be a rescue measure, too.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances)

ATC code: L01DB01

Doxorubicin is an anthracycline antibiotic. It exerts its antineoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). All of these have a deleterious effect on DNA synthesis: Intercalation of the doxorubicin molecule leads to an inhibition of RNA and DNA polymerases by way of disturbances in base recognition and sequence specificity. The inhibition of topoisomerase II produces single and double strand breaks of the DNA helix. Scission of DNA also originates from the chemical reaction with highly reactive oxygen species like the hydroxyl radical $\text{OH} \cdot$. Mutagenesis and chromosomal aberrations are the consequences.

The specificity of doxorubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastro-intestinal tract and gonads are the main normal tissues damaged.

An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance. In an attempt to overcome cellular resistance to doxorubicin, the use of calcium antagonists such as verapamil has been considered since the primary target is the cell membrane. Verapamil inhibits the slow channel of calcium transport and can enhance cellular uptake of doxorubicin. A combination of doxorubicin and verapamil is associated with severe toxic effects in animal experiments.

5.2 Pharmacokinetic properties

Following intravenous injection, doxorubicin is rapidly cleared from the blood, and distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. Relatively low but persistent levels are found in tumour tissue.

Doxorubicin undergoes rapid metabolism in the liver. Doxorubicinol is the most common metabolite, although a substantial fraction of patients forms doxorubicin-7-deoxyglycone and doxorubicinol-7-deoxyglycone. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is as unchanged drug. Only about 5 % of a dose is excreted in urine within 5 days. Doxorubicinol, the major (active) metabolite, is excreted in both bile and urine. It does not cross the blood-brain barrier, but does cross the placenta and is distributed into breast milk. The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes, 3.3 hours and about 30 hours.

The volume of distribution V_d is 25 l; the degree of protein binding is 60–70%. There is substantial interpatient variation in biotransformation. Clearance is apparently not dose-related, but it is higher in men than in women.

Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised although there is no clear relationship between liver function tests, doxorubicin clearance and clinical toxicity. Since doxorubicin and metabolites are excreted in the urine only to a minor degree, there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.

5.3 Preclinical safety data

Doxorubicin behaves as a typical inhibitor of cellular reproduction. Cytotoxicity to the most actively proliferating tissues is more prevalent and occurs earlier with respect to parenchymal damage.

1 Single dose toxicity

Intravenous LD₅₀ values in different animal species have been reported as follows:

Mouse 9 – 21 mg/kg, rat 8 – 14 mg/kg, rabbit 6 mg/kg and dog 2.5 mg/kg. A clear dose-dependent acute toxicity was observed.

2 Repeated dose toxicity

In clinical practice, the chronic toxicity of doxorubicin is rather similar to that of other comparable cytotoxic substances used in chemotherapy of malignant neoplasms. However, due to its cardiotoxic adverse effects doxorubicin notably warrants special precautions (cf. section 4.8.2.1).

Intravenous doses of 0.125 to 0.5 mg/kg/d were given to rabbits and dogs for 3 months. The lowest dose caused neither mortality nor other signs of toxicity (except for a mild inhibition of spermatogenesis). With the higher doses mortality, hemorrhagic enterocolitis, arrest or reduction of body growth, alopecia and melanosis, total depression of hemopoiesis with particular damage to the platelets, blood coagulation changes, hypoproteinemia, hyperazotemia, morphologic renal damage and depression of spermatogenesis was observed.

3 Tumorigenicity and mutagenicity

Single i.v. doses of doxorubicin induce mammary tumours in rats. It is also highly potent in producing malignant transformations and mutations in mammalian cell systems in vitro. In the Salmonella/microsome mutagenicity test system (Salmonella typhimurium + rat liver microsome S-9 fraction) doxorubicin proved to be a positive carcinogen. It is thus concluded that doxorubicin may have carcinogenic potential in man.

Doxorubicin proved to be mutagenic in the standard plate incorporation method of the Ames reversion test. Doxorubicin was also strongly mutagenic against the frameshift-sensitive strain TA98, especially when Cu⁺⁺ ions were present. In the dominant lethal heritable translocation and morphological specific locus test doxorubicin did not induce dominant lethal mutations in murine male germ cells but did

induce dominant lethal mutations in female oocytes. In the cytokinesis-block micronucleus assay, it demonstrated a significant increase in the rate of micronucleated cells and of chromosomal aberrations.

4 Toxicity to reproduction

With respect to fertility, embryonal and foetal toxicity clinical data in man are incomplete. A termination of pregnancy may not always be mandatory and can only be judged in individual cases. In any case, cardiologic and blood tests in the foetus or newborn child is strongly recommended. The risk of malformations and malfunctions in children is considered to be high. Doxorubicin has been found in foetal tissue (liver, kidney, lungs) at concentrations several times those in maternal plasma indicating that it passes the placenta. Doxorubicin proved to be highly teratogenic in rats and mutagenic in the Ames test. Pregnancy is therefore a contraindication for Doxorubicin Hydrochloride.

In animal experiments, toxic effects of doxorubicin on reproduction were observed. In the rat, doxorubicin is teratogenic after i.p. doses as low as 1.25 mg/kg/day. Characteristic malformations included oesophageal and intestinal atresia, tracheoesophageal fistula, hypoplasia of the urinary bladder and various cardiovascular anomalies. The frequency of anomalies rose sharply as the dose increased. At 2.25 mg/kg/day, all embryos were abnormal, and doxorubicin at 2.5 mg/kg/day led to resorption of all embryos. Teratogenicity in late organogenesis (reduction anomalies of the distal limbs) was also demonstrated in rat embryo cultures in the concentration range of 0.1 – 20 Mol/l.

In another experiment with female Sprague-Dawley rats, treated i.p. 1 - 10 mg/kg doxorubicin, the examination of the embryos revealed specific teratogenic effects on the caudal region. Histological examination showed signs of cell death at the level of the gut epithelium and bronchial bar mesenchyme. In the latter experiment, the highest dose of doxorubicin was maternolethal. The foetuses showed a dose-related increase of specific malformations of the digestive system (oesophageal and intestinal atresia, stomach hypoplasia.), urinary system (bladder agenesis or hypoplasia, hydronephrosis), and cardiovascular malformations.

The doxorubicin-treated foetal rat is an excellent model for studying the so-called VATER association (vertebral defects, anorectal anomaly, tracheoesophageal fistula with oesophageal atresia, and Radial dysplasia). Exposure of the rat foetus produces a spectrum of anomalies, including oesophageal atresia and other features of VATER association. Vertebral and rib anomalies e.g. were found in 54 % and limb anomalies in 35% of foetuses exposed to teratogenic doses of doxorubicin in utero.

In rats decreased weights of genital organs, an extremely decreased sperm count, a low sperm motility, a low implantation rate, a decreased number of spermatogonia and a decreased number of live foetuses were observed after 4 weeks of treatment with doses of 1 or 2 mg/kg. After 9 weeks of treatment, genital organs showed atrophy.

Doxorubicin was not teratogenic in the rabbit when given at i.v. doses up to 0.6 mg/kg/day, but a high incidence of abortion occurred.

In the chicken, doxorubicin is toxic and teratogenic during the period of early organogenesis of the chick embryos after eggs received a single injection on days 1 and 2 of incubation. Doxorubicin caused embryonic death, stunted growth, and various gross morphological malformations. LD50 values were 2.5 g/egg on day 1 and 0.9 g/egg on day 2.

5 Neurotoxicity

In ganglion cells of the peripheral nervous system and in spinal, paravertebral and trigeminal ganglia, loss of neurones was observed in rats after i.v. injections of 10 mg/kg. The animals developed severe posterior limb ataxia and mild ataxia of the forelimbs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium chloride
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin as a precipitate may form and it should not be mixed with 5-fluorouracil as degradation may occur. Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials: 2 years

Opened vials: The product should be used immediately after opening the vial.

Prepared infusion solutions:

Chemical and physical in-use stability has been demonstrated in sodium chloride 0.9 % and glucose 5 % for up to 48 hours at 2 – 8°C and for up to 24 hours at 25°C when prepared in glass containers protected from light.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

Colourless glass vials (type I glass) with nominal volumes of 5 ml, 10 ml, 25 ml, 75 ml or 100 ml.

Chlorobutyl rubber stoppers with ETFE layer.

Original pack containing 1 or 5 vial(s) of 5 ml / 10 ml / 25 ml / 75 ml / 100 ml each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

Any unused product or waste material should be disposed of in accordance with local requirements. Observe guidelines for handling cytotoxic drugs.

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 should wear protective clothing: goggles, gowns, disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed and absorbent paper.
- All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) incineration.
- In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not graze the skin by using a scrubbing brush.
- In case of contact with eye(s), hold back the eyelid(s) and flush the affected eyes with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably soaking overnight and then rinse with water.
- All cleaning materials should be disposed of as indicated previously.
- Always wash hands after removing gloves.

7 MARKETING AUTHORISATION HOLDER

medac Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstraße 3
20354 Hamburg / Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 22472/0003

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
01/04/2008
- 10** **DATE OF REVISION OF THE TEXT**
01/04/2008

Package Leaflet: Information for the patient

Doxorubicin hydrochloride 2 mg/ml solution for infusion**Read all of this leaflet carefully, before you receive this medicine.**

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

In this leaflet:

1. What Doxorubicin hydrochloride is and what it is used for
2. Before you receive Doxorubicin hydrochloride
3. How Doxorubicin hydrochloride is administered
4. Possible side effects
5. How to store Doxorubicin hydrochloride
6. Further information

1. What Doxorubicin hydrochloride is and what it is used for

Doxorubicin is one of a group of medicines known as anthracyclines. It works by killing tumour and blood cancer cells. Your doctor will be able to explain how doxorubicin might help in your particular condition.

2. Before you receive Doxorubicin hydrochloride You must not receive Doxorubicin hydrochloride in the following cases, please tell your doctor

- if you have ever had any hypersensitivity reaction to doxorubicin or any of the other ingredients of Doxorubicin hydrochloride or to other anthracyclines.
- if you have been told that your blood is thin (your bone marrow is not working well).
- if you have, or ever have had, any heart problems.
- if you have received doxorubicin, other anthracyclines, other anti-tumour drugs or immunosuppressive drugs before.
- if you tend to bleed easily.
- if you suffer from any kind of infection.
- if you suffer from mouth ulcers.
- if your liver is not working well.
- if you suffer from an infection of the bladder (in case the medicine is given to you by an administration into your bladder)

Take special care with Doxorubicin hydrochloride and tell your doctor

- if you have had any radiotherapy before.
- if you are pregnant, trying to become pregnant, likely to want to try to become pregnant in the future or if you want to father a child.
- if you are breast-feeding.
- if you are on a controlled sodium diet.

Using other medicines

Please inform your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The following medications can interact with Doxorubicin hydrochloride 2 mg/ml solution for infusion:

- Other cytostatics (medication against cancer) e.g. anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, dactinomycin, fluorouracil, mitomycin C, taxanes (e.g. paclitaxel), mercaptopurine, methotrexate, streptozocin
- Cardioactive drugs (medications for heart diseases), e.g. calcium channel blockers, verapamil, digoxin
- Inhibitors of cytochrome P-450 (drugs that stop the substance cytochrome P-450, which is important for the detoxification of your body, from working; e.g. cimetidine), drugs inducing cytochrome P-450 (e.g. rifampicin, barbiturates including phenobarbital)
- Antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate)
- Heparin (prevents the clotting of the blood)
- Amidopyrine derivatives (pain-killers), antiretroviral drugs



The following information is intended for the medical or healthcare professionals only:

Therapeutic indications

Antimitotic and cytotoxic. Doxorubicin has been used with success 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 of breast and lung. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma *in situ* and papillary tumours of the bladder, by intravesical administration.

(medications against special forms of viruses, e.g. AIDS), chloramphenicol and sulphonamides (medications against bacteria), progesterone (e.g. at threatening miscarriage), amphotericin B (drug used against fungal diseases)

- Live vaccines (e.g. polio(myelitis), malaria)

Please note that these statements may also apply to products used some time ago or at some time in the future.

Pregnancy and breast-feeding

It is known that doxorubicin passes the placenta and harms the foetus in animal experiments. Therefore doxorubicin must not be administered if you are pregnant. The drug also concentrates in human milk.

Your doctor will decide whether breast-feeding or the drug should be discontinued.

Women must not get pregnant during the treatment with Doxorubicin hydrochloride. If you get pregnant during treatment with Doxorubicin hydrochloride, please inform your doctor immediately.

During the treatment and until 6 months after the treatment was stopped you should use effective contraception regardless of whether the male or the female partner took Doxorubicin hydrochloride.

For safety reasons, men wanting a baby should preserve unexposed sperm prior to treatment with Doxorubicin hydrochloride.

Ask your doctor for advice before taking any medicine.

Driving and using machines

Do not drive because you possibly may become sleepy.

Important information about some of the ingredients of Doxorubicin hydrochloride

Please tell your doctor if you are on a low-sodium diet. He/she will take into account that 1 ml of Doxorubicin hydrochloride contains 3.5 mg sodium.

3. How Doxorubicin hydrochloride is administered**Method and routes of administration**

Do not administer the medicine yourself. Your medicine will be given to you as part of an intravenous infusion, into a blood vessel, under the direction of specialists. You will be monitored regularly both during and after your treatment.

If you suffer from superficial bladder cancer it is possible that you may receive your medicine into your bladder (intravesical use).

Dosage

The dosage is usually calculated on the basis of your body surface area. 60 - 75 mg per square metre of body surface area may be given every three weeks when used alone. The dosage may need to be reduced to 30 - 40 mg per square metre of body surface area when given in combination with other anti-tumour drugs. Alternatively the dosage may be calculated on body weight and given as either a single dose every three weeks or divided over three consecutive days (0.4 - 0.8 mg/kg or 20 - 25 mg per square metre of body surface area on each day). If given weekly the recommended dose is 20 mg per square metre of body surface area.

Your doctor will advise you of how much you will need.

Patients with reduced liver function

If your liver function is reduced, the dosage should be decreased. Your doctor will advise you of how much you need.

Children/Elderly or patients after radiotherapy

The dosage may need to be reduced in children and the elderly or if you have received any radiotherapy.

Transient ECG changes, such as T-wave flattening, S-T depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Precaution is also required during simultaneous or previous



The following information is intended for the medical or healthcare professionals only:

Therapeutic indications

Antimitotic and cytotoxic. Doxorubicin has been used with success 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 of breast and lung. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma *in situ* and papillary tumours of the bladder, by intravesical administration.

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic drugs.

Posology and method of administration

For intravenous use

The solution is given via the tubing of a freely running intravenous infusion of sodium chloride 0.9 % or dextrose 5 % into a large vein using a Butterfly needle, taking 2 to 3 minutes over the injection. This technique minimises the risk of thrombosis or perivenous extravasation, which can lead to severe local cellulitis and necrosis.

Dosage is usually calculated on the basis of body surface area. On this basis, a dose of 60 - 75 mg/m² body surface area is recommended every three weeks when doxorubicin is used alone. If using the body weight to calculate the dose, dosages of 1.2 - 2.4 mg/kg are recommended. If it is used in combination with other antitumour agents with overlapping toxicity, such as high-dose i.v. cyclophosphamide or related anthracycline compounds such as daunorubicin, idarubicin and/or epirubicin, the dosage of doxorubicin should be reduced to 30 - 40 mg/m² every three weeks.

Dividing the dose over three successive days (20 - 25mg/m² or 0.4 - 0.8mg/kg on each day) gives greater effectiveness at the cost of higher toxicity. Administration of doxorubicin in a weekly regimen has been shown to be as effective as the 3-weekly regimen. The recommended dosage is 20 mg/m² weekly, although objective responses have been seen at 6 - 12 mg/m². Weekly administration has been shown to be associated with reduced cardiotoxicity compared with a 3-weekly schedule.

Patients who have received prior radiotherapy to the mediastinal/pericardial area should not receive doxorubicin greater than a total cumulative dose of 400 mg/m².

Dosage may also need to be reduced in young children and the elderly. It is recommended that the total cumulative dose of doxorubicin for adults aged 70 or older be restricted to 450 mg/m² body surface area.

For intravesical use

Doxorubicin may be used by intravesical instillation for the treatment of superficial bladder carcinoma after transurethral resection. However, this method is contraindicated in invasive bladder tumours.

The patient should not drink fluids for 12 hours prior to the treatment.

25 ml of the solution, containing 50 mg of doxorubicin hydrochloride, is mixed under sterile conditions with 20 ml normal saline and instilled via catheter into the bladder.

After removal of the catheter, the patient stays lying on his back for 15 minutes.

At 15-minute intervals, the patient makes a quarter turn over a period of 1 hour. At the end of this period, the patient may void.

This procedure can be repeated at monthly intervals.

Impaired hepatic function

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

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

Contraindications

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

Doxorubicin hydrochloride is contra-indicated in patients with pre-existing myelosuppression (e.g. induced by previous antitumour treatment).

Dosage should not be repeated in the presence or development 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.

Doxorubicin hydrochloride is contraindicated in patients with impaired cardiac function and in patients who have been treated previously with complete cumulative doses of anthracyclines (see section Special warnings and precautions for use). In patients who have received anthracyclines previously, addition of further anthracycline therapy can be contemplated only after careful assessment of the cardiac status of the patient. The potential benefit of additional anthracycline therapy must carefully be weighed against the possible risks of cardiotoxicity.

Transient ECG changes, such as T-wave flattening, S-T depression and arrhythmias are not considered indications for suspension of doxorubicin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Precaution is also required during simultaneous or previous radiotherapy of the mediastinal/pericardial area or after treatment with other cardiotoxic substances.

Doxorubicin must not be given intrathecally or intramuscularly or by long-term infusion. Direct intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates the tissues. If a central vein catheter is used then infusion of doxorubicin in sodium chloride 0.9% injection is advised.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.

On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation. Even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein. In the event of inadvertent extravasation, ice packs should be applied to the injection site. Local injection of dexamethasone or hydrocortisone may be used to minimise local tissue necrosis. Hydrocortisone cream 1% may also be applied locally.

Careful haematological monitoring is required due to the myelosuppressive effects. Pre-treatment with digoxin (250 µg daily starting 7 days before doxorubicin) showed a protective effect against cardiotoxicity. In cases of hyperuricaemia, an application of xanthinoxidase-blocking drugs may be indicated.

Like all chemotherapy, therapy with doxorubicin hydrochloride should be carried out only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

This medicinal product contains 3.5 mg sodium per 1 ml of doxorubicin hydrochloride solution for infusion. This should be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

Concurrent administration of other antineoplastic agents, e.g.: anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclosporin, cytarabine, dacarbazine, daclinomycin, fluorouracil, mitomycin C and taxanes can potentiate the risk of doxorubicin-induced congestive heart failure.

The disposition of doxorubicin was found to be significantly altered when it was administered immediately after a short intravenous infusion of paclitaxel. The co-administration of paclitaxel causes a decreased clearance of doxorubicin and more neutropenic and stomatitis episodes have been observed.

Increased cardiotoxicity has also been reported after simultaneous intake of cardioactive drugs, e.g., calcium channel blockers and verapamil (with an increase of doxorubicin peak levels, terminal-half life and volume of distribution). The bioavailability of digoxin decreases during doxorubicin therapy. Careful monitoring of the heart function is required in all such concomitant therapeutic regimens.

Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects, especially in cardiotoxicity. Drugs inducing cytochrome P-450 (e.g. rifampin, barbiturates including phenobarbital) may increase the metabolism of doxorubicin, possibly decreasing the efficacy of doxorubicin.

If doxorubicin therapy is followed by administration of cyclophosphamide, an increased rate of haemorrhagic cystitis has been reported.

The absorption of antiepileptic drugs (e.g. carbamazepine, phenytoin, valproate) is decreased after concomitant use of doxorubicin.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Co-administration of heparin and doxorubicin can lead to an increase in the rate of doxorubicin clearance. Furthermore, precipitates may form and lead to a loss of efficacy of both drugs (see section Incompatibilities).

Disturbed haematopoiesis has been observed after co-administration of substances influencing the bone-marrow function (e.g. amidopyrine derivatives, antiretroviral drugs, chloramphenicol, phenytoin, sulphonamides). Increased neutropenia and thrombocytopenia have been reported after simultaneous use of progesterone. Marked nephrotoxicity of Amphotericin B can occur during doxorubicin

Dosage should not be repeated in the presence or development 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.

Doxorubicin hydrochloride is contraindicated in patients with impaired cardiac function and in patients who have been treated previously with complete cumulative doses of anthracyclines (see section Special warnings and precautions for use). In patients who have received anthracyclines previously, addition of further anthracycline therapy can be contemplated only after careful assessment of the cardiac status of the patient. The potential benefit of additional anthracycline therapy must carefully be weighed against the possible risks of cardiotoxicity.

Doxorubicin hydrochloride is further contraindicated in patients with increased haemorrhagic tendency, stomatitis, generalised infections, markedly impaired liver function and cystitis (in the case of intravesical application).

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, but this condition could even occur with doses of 240 mg/m². These effects may occur during infusion, but also several weeks after termination of therapy.

Cardiac failure may not respond to treatment. Early clinical diagnosis of drug-induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest.

Severe cardiac toxicity may occur precipitously without antecedent ECG changes. Base line ECG and periodic follow up ECG during and immediately after active drug therapy is an advisable precaution.

Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Co-administration of heparin and doxorubicin can lead to an increase in the rate of doxorubicin clearance. Furthermore, precipitates may form and lead to a loss of efficacy of both drugs (see section Incompatibilities).

Disturbed haemotopoiesis has been observed after co-administration of substances influencing the bone-marrow function (e.g. amidopyrine derivatives, antiretroviral drugs, chloramphenicol, phenytoin, sulphonamides). Increased neutropenia and thrombocytopenia have been reported after simultaneous use of progesterone.

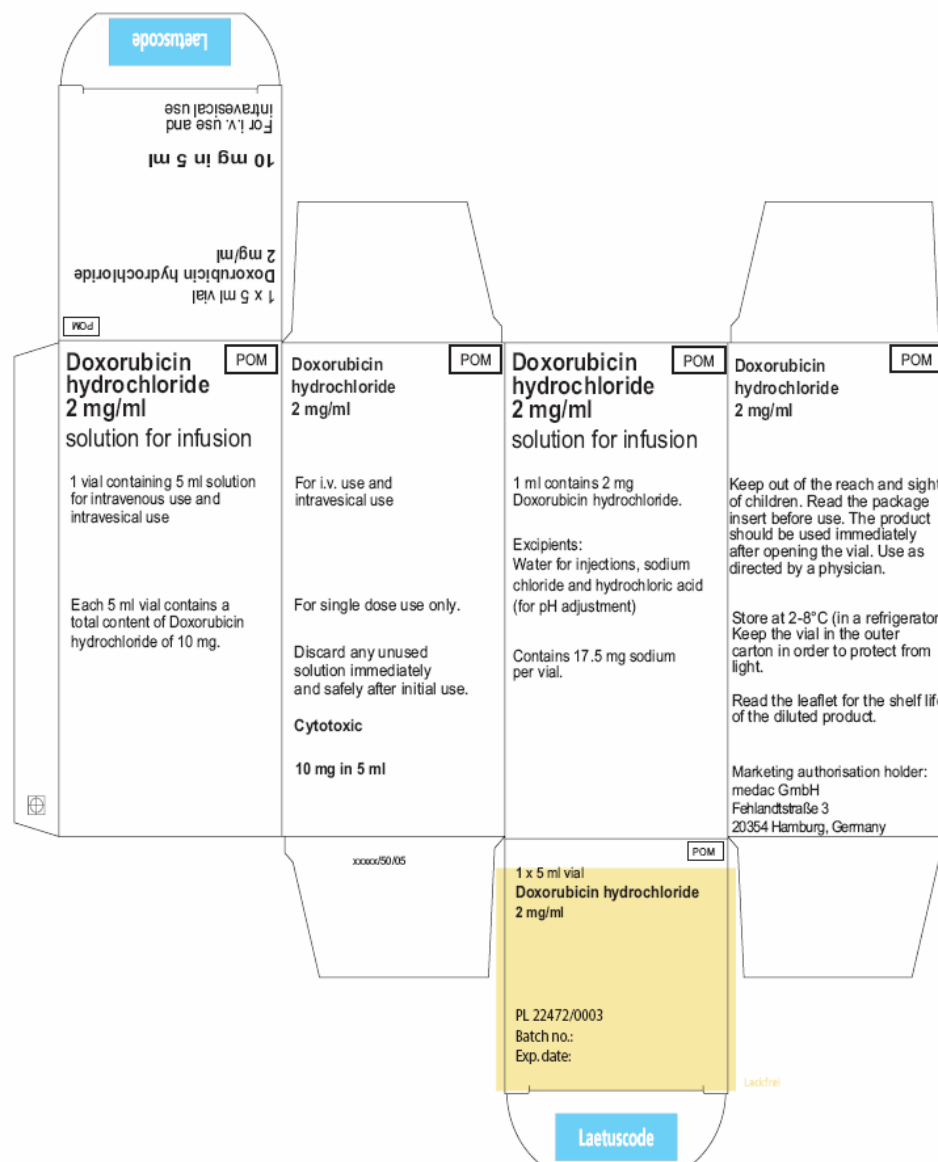
Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

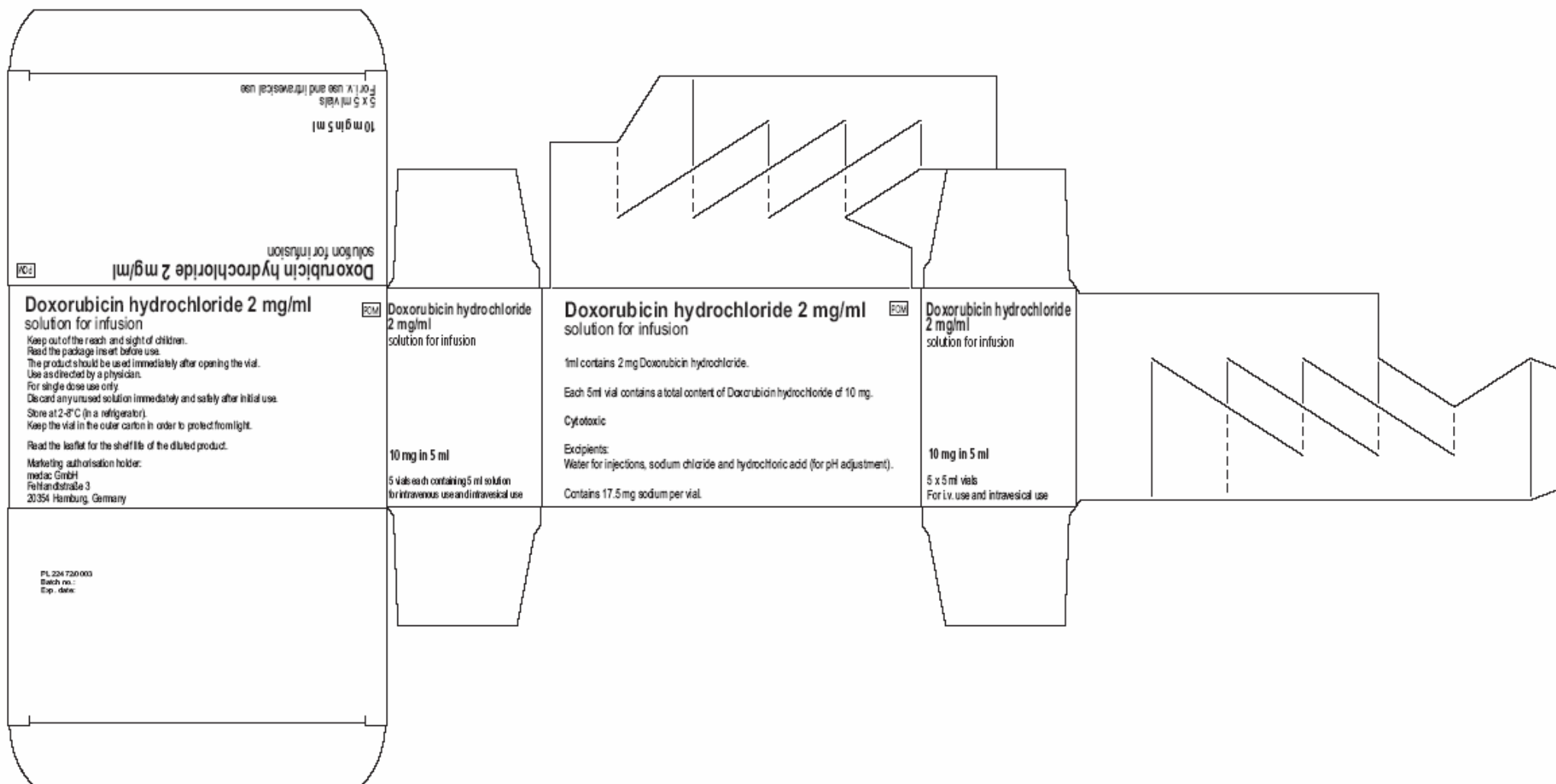
Live vaccines must not be used during doxorubicin therapy due to the risk of generalised disease, which may be lethal. The risk is increased in patients who are immunodepressed due to the underlying disease.

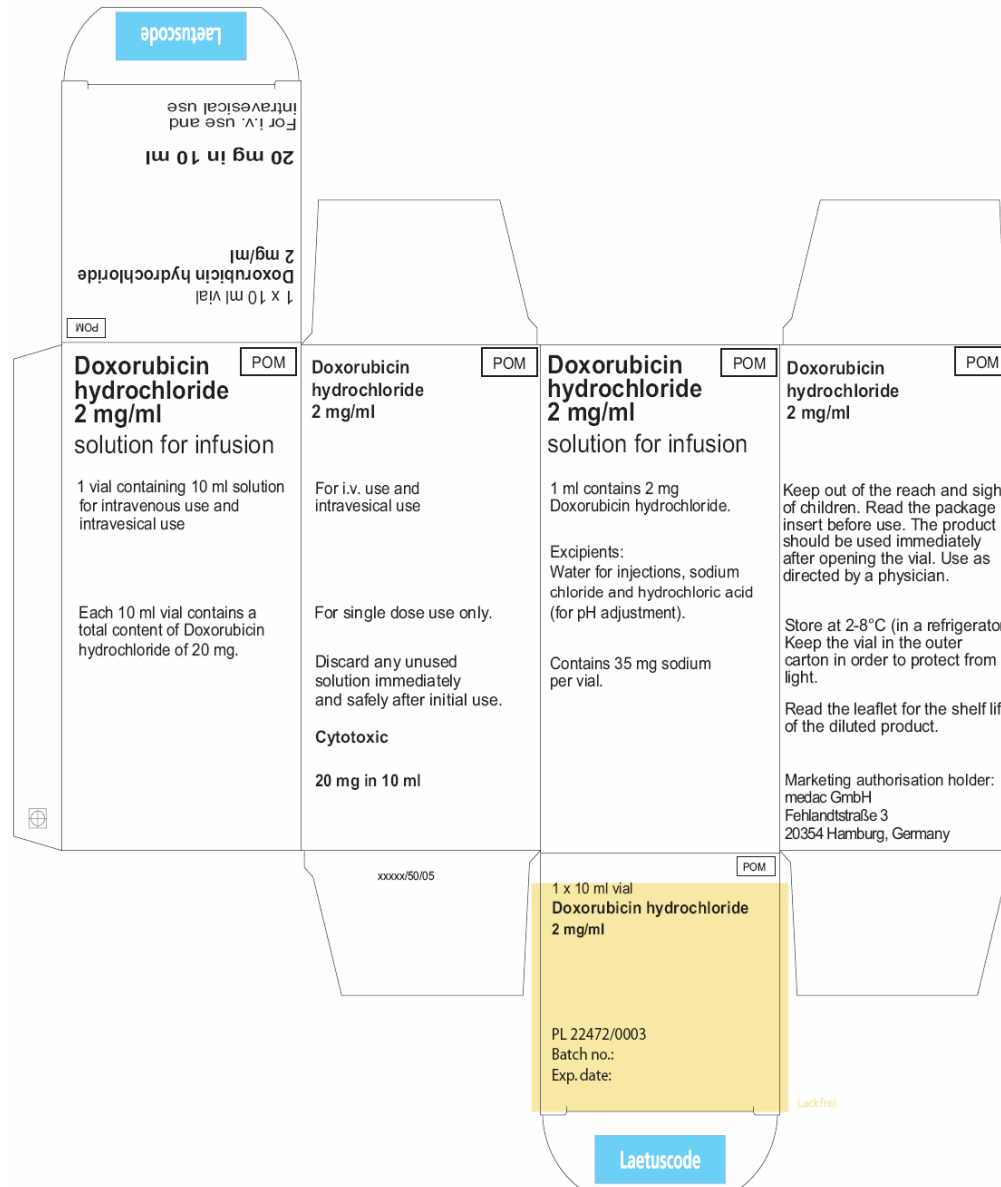
Undesirable effects

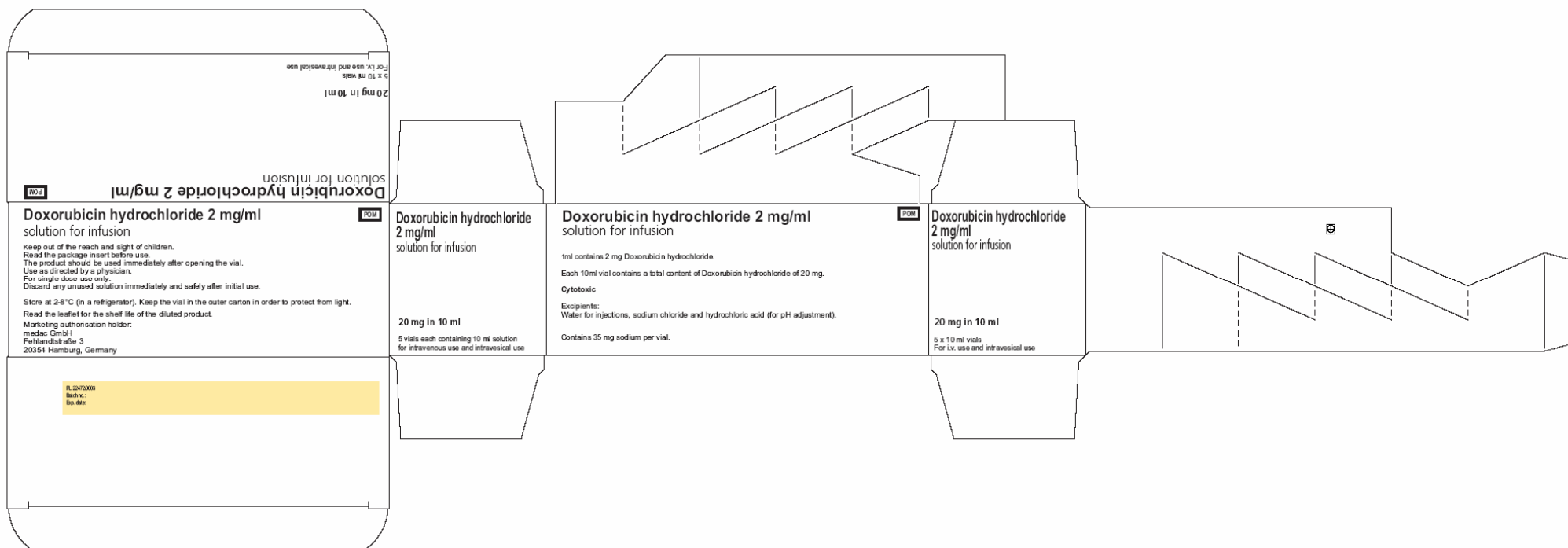
General

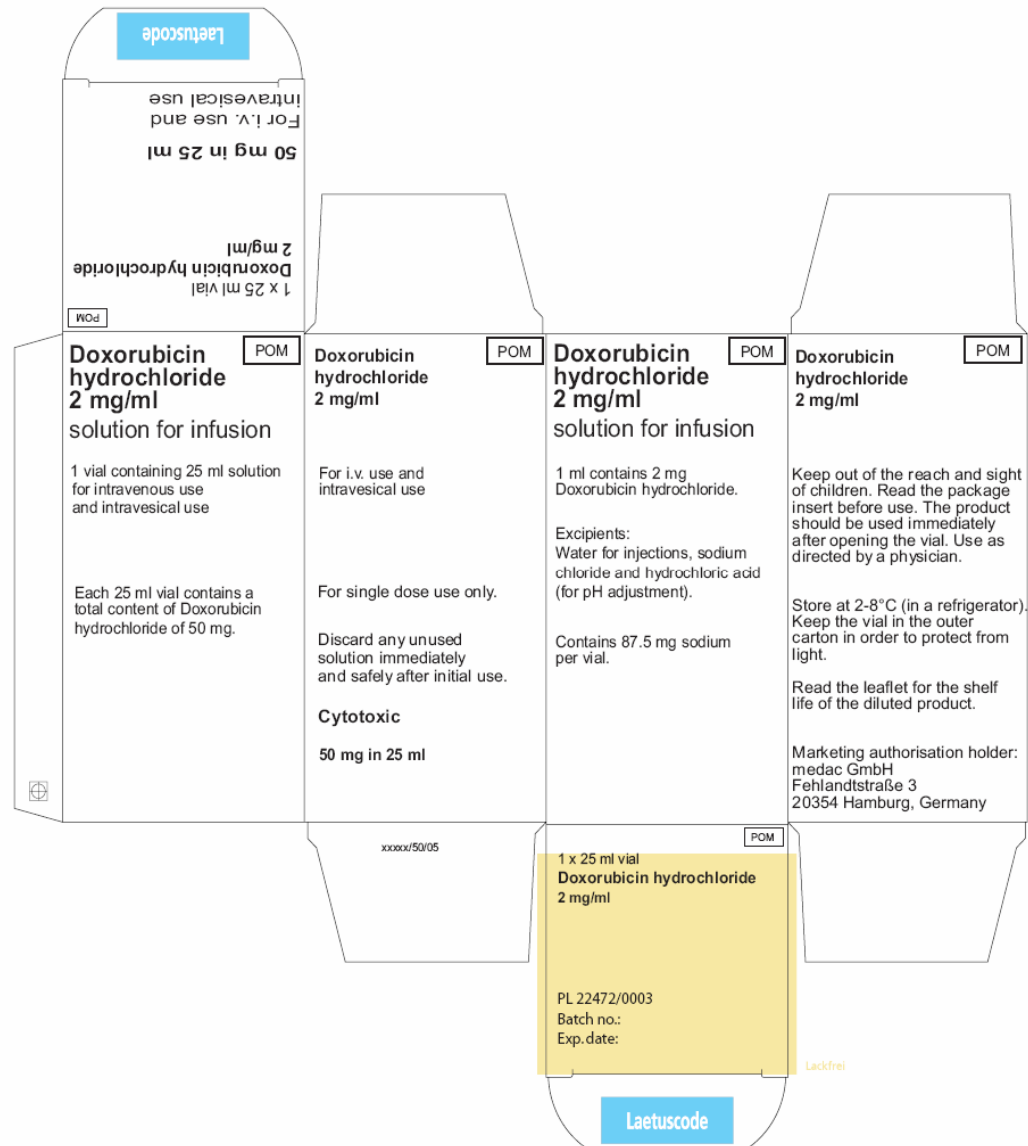
Bone Marrow Depression (myelosuppression): There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leukopenia is usually transient, reaching its nadir at 10 – 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as 1000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed.

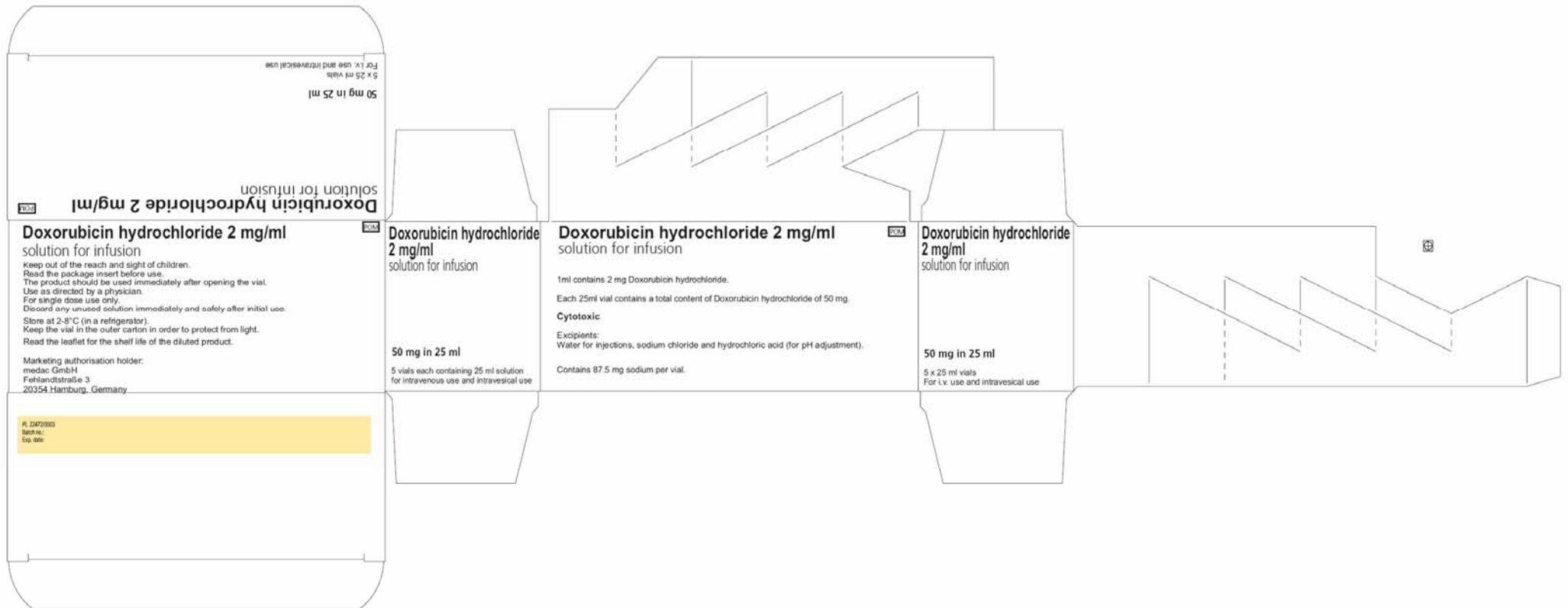


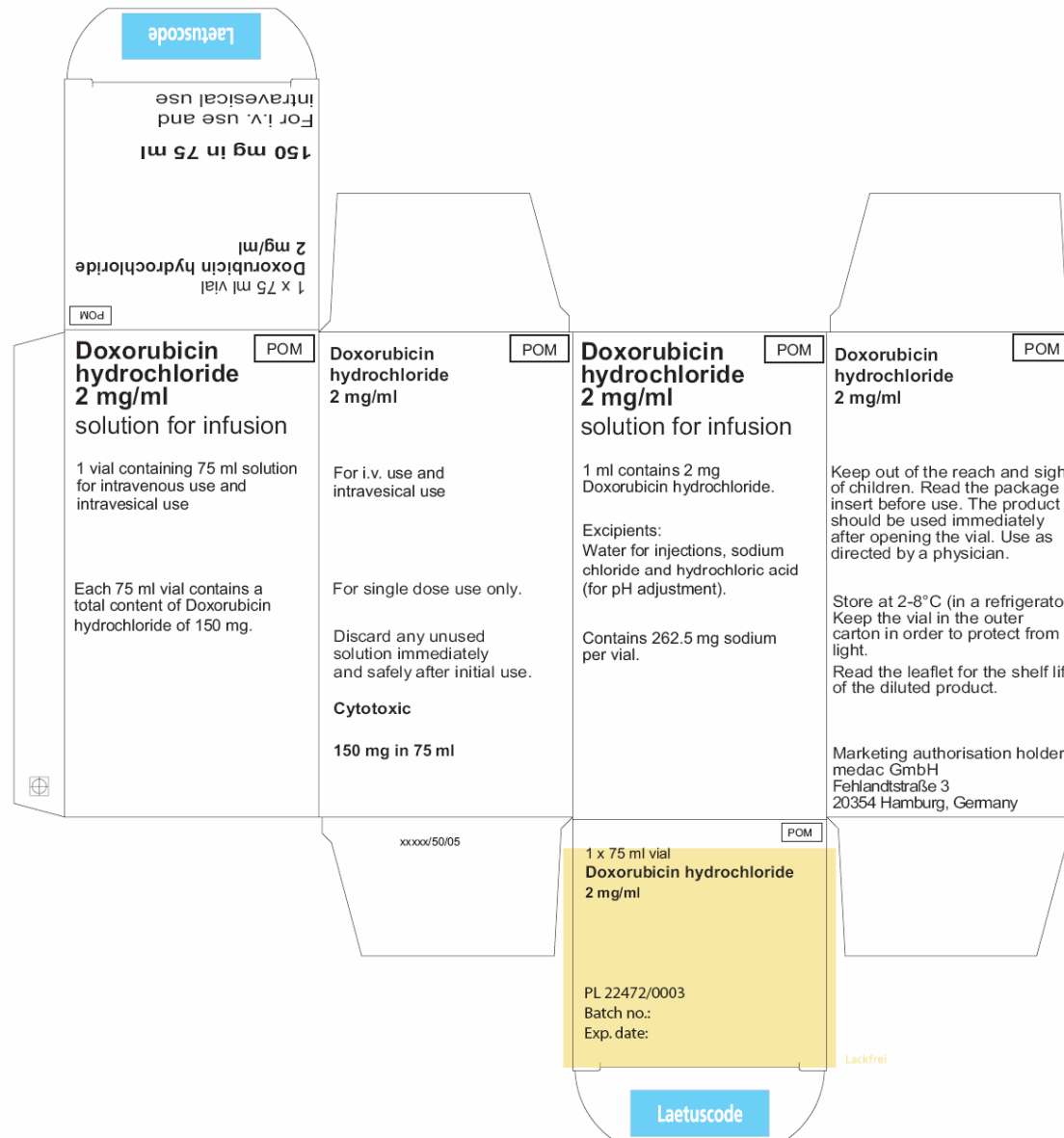


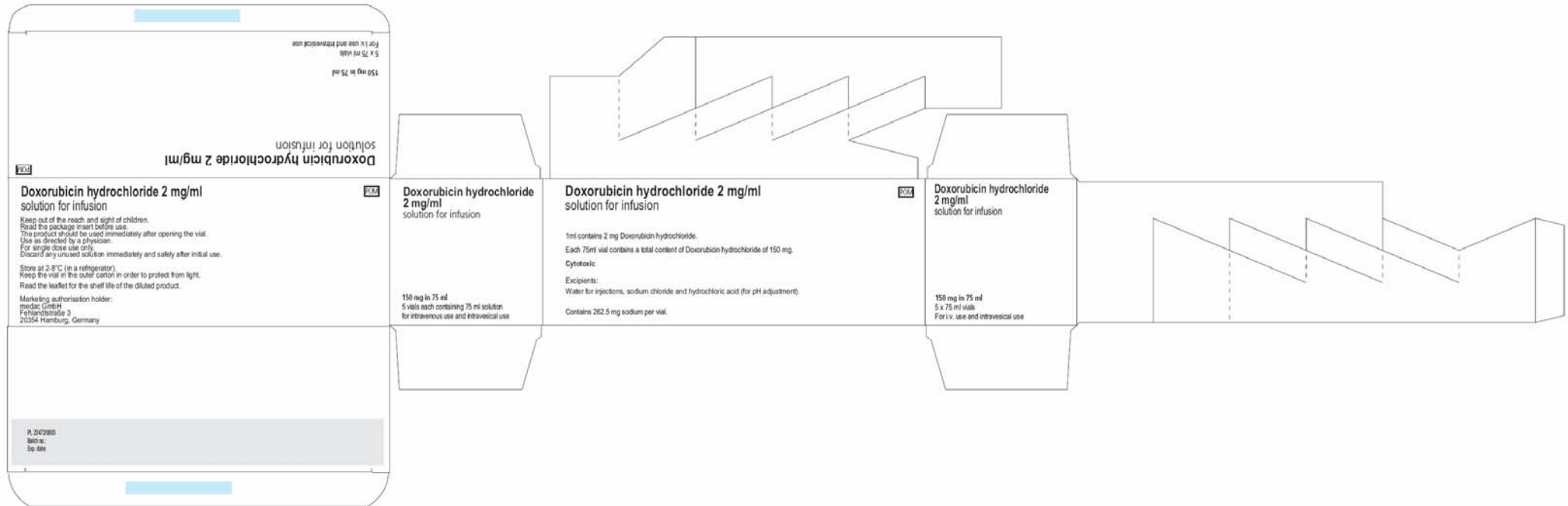












Doxorubicin hydrochloride 2 mg/ml solution for infusion

50 mg in 25 ml

Cytotoxic

For intravenous use and intravesical use

1ml contains 2 mg Doxorubicin hydrochloride.

Each 25ml vial contains a total content of Doxorubicin hydrochloride of 50 mg.

Other ingredients: Water for injections, sodium chloride, hydrochloric acid (for pH adjustment).

Contains 87.5 mg sodium per vial.

Keep out of the reach and sight of children. Read the package insert before use. The product should be used immediately after opening the vial. Use as directed by a physician. For single dose use only. Discard any unused solution immediately and safely after initial use.

Store at 2 - 8°C (in a refrigerator). Keep the vial in the outer carton in order to protect from light.

Read the leaflet for the shelf life of the diluted product.

medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany

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PL 22472/0003

Batch no.:

Exp. date:

Doxorubicin hydrochloride 2 mg/ml solution for infusion

150 mg in 75 ml

Cytotoxic

For intravenous use and intravesical use

1ml contains 2 mg Doxorubicin hydrochloride.

Each 75ml vial contains a total content of Doxorubicin hydrochloride of 150 mg.

Other ingredients: Water for injections, sodium chloride, hydrochloric acid (for pH adjustment).

Contains 262.5 mg sodium per vial.

Keep out of the reach and sight of children. Read the package insert before use. The product should be used immediately after opening the vial. Use as directed by a physician. For single dose use only. Discard any unused solution immediately and safely after initial use.

Store at 2 - 8°C (in a refrigerator). Keep the vial in the outer carton in order to protect from light.

Read the leaflet for the shelf life of the diluted product.

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Batch no.:

Exp. date:

Doxorubicin hydrochloride 2 mg/ml solution for infusion

200 mg in 100 ml

Cytotoxic

For intravenous use and intravesical use

1ml contains 2 mg Doxorubicin hydrochloride.

Each 100ml vial contains a total content of Doxorubicin hydrochloride of 200 mg.

Other ingredients: Water for injections, sodium chloride, hydrochloric acid (for pH adjustment).

Contains 350 mg sodium per vial.

Keep out of the reach and sight of children. Read the package insert before use. The product should be used immediately after opening the vial. Use as directed by a physician. For single dose use only. Discard any unused solution immediately and safely after initial use.

Store at 2 - 8°C (in a refrigerator). Keep the vial in the outer carton in order to protect from light.

Read the leaflet for the shelf life of the diluted product.

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POM

PL 22472/0003

Batch no.:

Exp. date: