Public Assessment Report

DOXORUBICIN HYDROCHLORIDE 2MG/ML SOLUTION FOR INFUSION

PL 05041/0016

Applicant: hameln pharmaceuticals gmbh
DOXORUBICIN HYDROCHLORIDE 2MG/ML SOLUTION FOR INFUSION
PL 05041/0016

LAY SUMMARY

The MHRA has granted Hameln Pharmaceuticals GmbH a Marketing Authorisation (licence) for the medicinal product Doxorubicin Hydrochloride 2mg/ml Solution for Infusion (PL 05041/0016) 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 05041/0016) to Hameln Pharmaceuticals GmbH 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:

![Structure Diagram]

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 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 ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 3rd December 2001</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 28th January 2002</td>
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<td>The applications were determined on 1st April 2008</td>
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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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:

<table>
<thead>
<tr>
<th>Serum Bilirubin Levels</th>
<th>Bromsulphophthalein Retention</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>1.2 – 3.0 mg/100ml</td>
<td>9 - 15%</td>
<td>50% normal dose</td>
</tr>
<tr>
<td>&gt; 3.0 mg/100ml</td>
<td>&gt;15%</td>
<td>25% normal Dose</td>
</tr>
</tbody>
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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, daunorubicin, 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 haemopoiesis 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, leukenopenia 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 topoisoasmerase 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 OH • . 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-deoxyaglycone and doxorubicinol-7-deoxyaglycone. 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 Vd 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, cardiology 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 asep

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 vial of 5 ml / 10 ml / 25 ml / 75 ml / 100 ml.

Original pack containing 5 vials of 25 ml each.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling
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
Hameln Pharmaceuticals GmbH
Langes Feld 13
31789 Hameln / Germany
8 MARKETING AUTHORISATION NUMBER(S)
   PL 05041/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   01/04/2008

10 DATE OF REVISION OF THE TEXT
    01/04/2008
Doxorubicin Hydrochloride 2 mg/ml Solution for Infusion UKPAR PL 05041/0016

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. Also, read the leaflet every time you receive the medicine. If you have any further questions, please ask your doctor or 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 you think that you may have too many of this medicine in your body, or if the effects become 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. Information about 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 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 if:
- You have had an allergic reaction to doxorubicin or any of the other ingredients of Doxorubicin Hydrochloride or to other anthracyclines.
- You have been told that your blood is thin (your blood platelets are not working well).
- You have, or ever have had, any heart problems.
- You have received doxorubicin, other anthracyclines, or other antineoplastic drugs or immunosuppressive drugs before.
- You tend to bleed easily.
- You suffer from any kind of infection.
- You suffer from mouth ulcers.
- Your liver is not working well.
- You suffer from an infection of the bladder (in case the medicine is given to you by an in-dwelling catheter into your bladder).

3. How Doxorubicin Hydrochloride is administered

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

The following medicines can interact with Doxorubicin Hydrochloride 2 mg/ml solution for infusion:
- Cancer chemotherapy (medications against cancer, e.g. anthracyclines (daunorubicin, epirubicin, idarubicin), cisplatin, cyclophosphamide, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, mitomycin C, staudeson e.g. dacarbazine, metothrexate, vincristine).

4. Possible side effects

Please tell your doctor if you are on a low-sodium diet. This medicine may cause a lack of appetite, loss of appetite, nausea, vomiting, diarrhea, constipation, mouth ulcers.

If you are given the medicine by an in-dwelling catheter into your bladder,

5. Information about Doxorubicin Hydrochloride

Driving and using machines
Do not drive because you possibly may become sleepy.

6. Further information

Important information about some of the ingredients of Doxorubicin Hydrochloride

Doseage
The dosage is usually calculated on the basis of your body surface area.

For patients with reduced liver function
If your liver function is reduced, the dosage should be decreased.

Children/Infants or patients after radiation therapy
The dosage may not be reduced in children and the safety of this medicine in children has not been studied.

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Doxorubicin Hydrochloride 2 mg/ml Solution for Infusion UKPAR PL 05041/0016

**Therapeutic indications**

Antineoplastic and cytoplastic. Doxorubicin has been used with success to produce regression in a wide range of neoplastic conditions including acute leukemias, lymphomas, soft-tissue sarcomas, small cell lung carcinoma, pediatric malignancies, and adult solid tumours, in particular of breast and lung. Doxorubicin has also been used in the treatment of non-metastatic transitional cell carcinoma, carcinoma-in-situ and papillary tumours of bladder, by intravesical administration. Doxorubicin is frequently used in combination chemotherapy regimens with other cytotoxic drugs.

**Pharmacology 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% in water by means of a butterfly needle, taking 2 to 3 minutes over the injection. This technique minimizes the risk of extravasation or venous stasis, which can lead to severe local cellulitis and necrosis.

Doxorubicin is usually calculated on the basis of body surface area. This dose, a dose of 70-72 mg/m² body surface area per week, or every three weeks when chemotherapy is used alone. Using the body-weight to calculate the dose, closeovers of 2-3 mg/m² are recommended. It is used in combination with other antineoplastic agents with overlapping toxicity, such as mitomycin c, cyclophosphamide or related anthracine derivatives such as daunorubicin, idarubicin, or aclacinomycin A. The dosage of doxorubicin should be reduced to 30-40 mg/m² every three weeks.

Doxorubicin may be given over three consecutive days (20-25 mg/m² per day) or 5-7.5 mg/m² per day for five consecutive days. In some cases, a total dose of 100-150 mg/m² may be given over a period of 30 days. However, the maximum single dose should not exceed 30-40 mg/m².

**Contraindications**

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

**Dosage and administration**

Doxorubicin hydrochloride is contraindicated in patients with pre-existing heart disease (i.e. induced by previous treatment).

Dosage should not be repeated in the presence or development of bone marrow suppression or cardiac affection. The latter may be prevented by prophylactic cyclophosphamide and prednisolone 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 exposed to anthracyclines (see section Special Warnings and Precautions for use). In patients who have received anthracyclines previously, doxorubicin should be contraindicated only after cardiac assessment of the cardiac status of the patient. The potential benefit of starting anthracyclines in these cases may be obtained by careful surveillance of cardiac function and careful assessment of the potential risk of cardiotoxicity.

Doxorubicin hydrochloride is further contraindicated in patients with increased haematology, liver, thyroid or diabetes.

**Special warnings and precautions for use**

A cumulative dose of 450-500 mg/m² should not be exceeded with extreme caution. Above this level, the risk of severe congestive cardiac failure increases greatly, but this condition can occur even with doses of 200-250 mg/m². Cardiac effects may occur during infusion, but also several years after termination of therapy.

Cardiac effects do not respond to treatment. Early clinical diagnosis of drug-induced heart failure appears to be essential in this type of treatment with drugs, such as doxorubicin, that are restricted in the heart. Doxorubicin hydrochloride will not cross the placenta. Maternal drug appears to occur in the amniotic fluid and be transferred to the fetus. The drug may be excreted in breast milk. Renal function should be monitored during therapy. Tumour lysis syndrome may occur after treatment.

**Precautions for use**

Transient ECG changes such as T-wave flattening, 5-T inverted T wave and QRS widening are not considered indications for cessation of doxorubicin therapy.

**When to discontinue therapy**

A persistent reduction in the voltage of the QRS complex is presently considered more specifically predictive for cardiomyopathy. If this occurs, the benefit of continued therapy must be carefully weighed against the risk of producing irreversible cardiac damage.

Precaution is also required during simultaneous or previous irradiation of the myocardium or lung or other therapy with other cardiotoxic substances.

Doxorubicin must not be given intravenously, intramuscularly or by oral administration.

**Effect on fertility**

Doxorubicin is excreted in breast milk. The drug appears to occur in the amniotic fluid and be transferred to the fetus. The drug may be excreted in breast milk. Renal function should be monitored during therapy. Whole body or regional irradiation may result in irreversible reproductive damage.

**Clinical trials**

Doxorubicin hydrochloride is used in the treatment of neoplastic diseases. The drug is also used in the treatment of neoplastic diseases. The drug is also used in the treatment of neoplastic diseases. The drug is also used in the treatment of neoplastic diseases.
If you received more Doxorubicin Hydrochloride than you should:

During and after treatment you will be carefully monitored by your doctor or nurse. The symptoms of an overdose are an extension of doxorubicin’s possible side effects, particularly the blood changes and heart problems. Heart disorders may even occur up to six months after you received the medicine. In case of an overdose your doctor will take appropriate measures, such as a blood transfusion and/or treatment with antibiotics. Please tell your doctor if any of the symptoms occur.

Effects of treatment with Doxorubicin Hydrochloride are Interpreted or stopped early:

Your doctor will decide the duration of your treatment with Doxorubicin Hydrochloride. If the treatment is stopped before the advised course of treatment is finished, the effects of the doxorubicin therapy might be reduced. Ask your doctor to advise if you want to stop the treatment.

Possible side effects:

Like all medicines Doxorubicin Hydrochloride can cause side effects, although not everybody gets them:

- Your urine may be coloured red, particularly the first time that you pass urine after each injection of Doxorubicin Hydrochloride. This is nothing to worry about and your urine will soon return to its normal colour.
- Blood changes – e.g. your vulnerability for infections may increase, you may suffer from unusual swellings and you may observe signs of anaemia (weakness, breathlessness, laboured breathing with a feeling of oppression). You may become less able to fight infections during the time you receive Doxorubicin Hydrochloride. Although abdominal and menstruation appear to return after termination of therapy, it is not proven that male patients become fertile again. For safety reasons men wishing a baby should preserve unpreserved semen prior to medication. According to the pregnant and up to six months after treatment with Doxorubicin Hydrochloride:
- Heart problems - for example you may notice your heart beating abnormally quickly, with an increase in pulse rate. In case of heart problems, routine ECG monitoring is considered advisable. If you have suffered from heart problems (even a long time ago) before treatment with Doxorubicin Hydrochloride make sure to tell your doctor about this.
- You may also lose your hair, and your beard may stop growing. Hair growth normally resumes after doxorubicin treatment is stopped.
- Myelosuppression - nausea and vomiting, lack of appetite - inflammation of the mucosa membranes (mouth, bowel, gall, stomach, rectum, pharynx)
- Rash and itching may develop at the site of injection. In this case we are recommended that your doctor should inform the specialist oncology one person. The injection should be stopped and replaced at another site.
- Facial flushing (if an injection has been given too slowly).
- Dehydration - Doxorubicin, like similar medicines, can occasionally itself cause bone marrow or kidney failure if used in combination with other anticancer agents.

Less frequent side effects of Doxorubicin hydrochloride are:

- Skin rash, separation and increased colouration of nails.
- Allergic reactions.
- Sweating.
- Constrictions, floods of tears.
- Damage to the kidneys.

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

5. How to store Doxorubicin Hydrochloride

Keep out of the reach and sight of children.

Do not use Doxorubicin Hydrochloride after the expiry date

which is stated on the label and carton. The expiry date refers to the last day of that month.

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

This product should be used immediately after opening the vial.

For single dose use only. Any unused solution should be discarded immediately after initial use. Do not use Doxorubicin Hydrochloride if you notice that the solution is not clear, red and free of particles.

In order to protect the environment medicines should not be disposed of via wastewater or household waste.

6. Further information

What Doxorubicin Hydrochloride contains:

Each 1 ml contains 2 mg doxorubicin hydrochloride.

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

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

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

Each 50 ml contains a total content of Doxorubicin hydrochloride of 100 mg.

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

The other ingredients are sodium chloride, hydrochloric acid (for pH adjustment) and water for injection.

What Doxorubicin hydrochloride looks like and contents of the pack:

Doxorubicin hydrochloride is a clear, red solution which is practically free of particles.

Packaging:

The solution is available in packages of 1 vial containing 510/25/50 or 100 ml solution or in packs of 8 vials containing 25 ml solution. This corresponds to 1020/150 or 200 mg of the active substance, doxorubicin hydrochloride, per vial.

Use all parts where may be relevant.

Marketing Authorisation holder and Manufacturer:

Marketing Authorisation Holder:

Heraeus pharmaceuticals G.2.3.1 D-75997 Hannover, Germany

Manufacturer:

Heraeus pharmaceuticals G.2.3.1 D-75997 Hannover, Germany

For any information about this document, please contact the local representative of the Marketing Authorisation Holder:

Heraeus pharmaceuticals G.2.3.1 D-75997 Hannover, Germany

This leaflet was approved in [MM/YYYY].
Doxorubicin Hydrochloride 2 mg/ml Solution for Infusion UKPAR PL 05041/0016

Ammonia suppression: Doxorubicin is a tubulin polymerisation-inhibiting agent; appropriate measures should be taken to prevent secondary infections.

Enhanced toxicity: It has been reported that doxorubicin may enhance the severity of the toxicity of other antineoplastic agents, such as cisplatin. Induced haemorrhagic cysts, myelosuppression induced by radiotherapy, hypereosinophilia of Eosinophils and the toxicity of streptomycin or methcortrope (see section Interactions).

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

Hepatic lesions: Toxicity to recommended doses of doxorubicin is enhanced by impaired liver function. Therefore, liver function test and laboratory evaluation of hepatic function should be carried out prior to and during the treatment. Doxorubicin is not recommended as a dose to patients concurrently treated with doxorubicin in association with DNA damaging anti-neoplastic agents. Such patients should have a short (1-3 year) latency period.

Adverse reactions

More frequent reactions

Cardiovascular: Cardiac dysfunction, congestive heart failure, supraventricular arrhythmias. Routine ECG monitoring is recommended and patients should be educated to report moderate or severe chest pain. Severe cardiac failure may occur suddenly, without prior warning and ECG changes.

Respiratory system

Pulmonary oedema

Skin reactions

Eruptions, mild or severe, urticaria, vasculitis, pruritus, erythema, erythema nodosum, progressing along the veins prior to the site of injection. Where aspiration occurs frequently, including the intravascular use of saline, gas or air may result in a normocytic normochromic anemia. Vascular dilation.

General

Dysphagia, facial flushing of the injection site may be prevented by following the procedure for administration recommended above (see section Precautions and method of administration).

Hypersensitivity

Nausea and vomiting, myasthenia gravis (muscle atrophy and oedema), diarrhoea, anaemia, ulceration and necrosis of the mucosa. Muscular atrophy is a frequent and painful complication of doxorubicin treatment. It is more commonly developed in the first 30 days, after treatment, and typically begins as a burning sensation in the mouth and pharynx. It may progress to the neck, chest and epigastrium, and progress to ulceration with risk of secondary infection and usually subsides in 10-15 days. Reversible impairment of the heart with cardiomyopathy is rare. Mucosal ulceration suggests that it is less frequent as the transition between doses increase. Muscular atrophy may be evident in patients who have had previous irradiation to the mucosa.

Other side effects

Gastrointestinal

Nausea and vomiting

Neurological

Cataracts, somnolence, abnormal dreams, depression, and peripheral neuropathy.

Dermatological

Urticaria, pruritus, hyperpigmentation.

Other side effects

Infections

Optic neuritis

Extrapyramidal symptoms

Oesophagitis

Urinary tract

Nephrotoxicity

Hepatic toxicity

Bone marrow suppression

Myelosuppression, myelopathy, myalgia, and shortness of breath, cyanosis, and hypoxia.

Miscellaneous

Hair loss, weight gain, appetite loss, mood swings, and anorexia.

Vascular

Venous thrombosis, deep vein thrombosis, pulmonary embolism.

Incompatibilities

Doxorubicin is not mixed with hemoglobin as a preservative for storage and it should not be mixed with 5-fluorouracil as degradation may occur. For long contact with any solution of an alkaline pH should be avoided as it will result in precipitation of the drug. In the absence of compatibility studies, the medicinal product must not be mixed with other medicinal products.

Preparation of solutions for infusion

Chemical and physical stability has been demonstrated in solution containing 0.9% glucose for at least 24 hours at room temperature. Dose may be obtained in this solution and stored at room temperature for the duration of the infusion. From a microbiological point of view, the product should be used immediately. If not used immediately, stored in refrigerator at 2-8°C. After opening the vial, store in refrigerator at 2-8°C. Doxorubicin solutions may be stored in the dark and kept under refrigeration at 2-8°C, unless diluted and stored in controlled and validated refrigerated conditions.

Special precautions for disposal and handling

For single use only.

Any unused vial or remaining vial 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:

- Personal protective equipment should be worn as a standard practice for handling.
- Personal protective equipment should be used for the duration of the session.
- Appropriate personal protective equipment should be used to avoid accidental exposure to the drug.
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