

**1. TRADE NAME OF THE MEDICINAL PRODUCT**

Doxorubin 0.2%.

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Doxorubin 0.2% injection contains doxorubicin hydrochloride  
2 mg/ml.

**3. PHARMACEUTICAL FORM**

Solution for Injection.

**4. CLINICAL PARTICULARS**

4.1 Therapeutic indications

In combination with other antineoplastic drugs, doxorubicin is intended for the treatment of acute lymphocytic leukaemia, except acute lymphatic leukaemia of low risk in children, acute myeloid leukaemia (Hodgkin- and non-Hodgkin lymphomas) osteosarcoma, Ewing sarcoma, adult soft tissue sarcoma, metastatic breast carcinoma, gastric carcinoma, small-cell lung cancer, neuroblastoma, Wilms tumour and bladder carcinoma.

Doxorubicin may be used intravesically as single agent for treatment and prophylaxis of superficial bladder carcinoma.

4.2 Posology and method of administration

Dosage depends on tumour type, hepatic function and concurrent chemotherapy.

The commonly recommended dosage schedule as a single agent is 60-75 mg/m<sup>2</sup> by intravenous injection, once every 3 weeks. An alternative dose schedule is 20 mg/m<sup>2</sup> intravenously, on 3 consecutive days, once every 3 weeks.

In combination with other cytotoxic agents doses of 50-75 mg/m<sup>2</sup> are administered.

Myelosuppression may be more pronounced because of the additive effects of the drugs.

The risk of development of cardiomyopathy gradually increases with the dosage. A cumulative dose of 550 mg/m<sup>2</sup> should not be exceeded. The administration of doxorubicin should be monitored by electrocardiography, echocardiography and carotid pulse curve: when the voltage of the QRS wave decreases by 30% or at a fractional shortening of 5% it is recommended that treatment is stopped.

If a patient received mediastinal irradiation, has concomitant heart disease, or is also treated with other cardiotoxic, non-anthracycline cytotoxic agents, a maximal cumulative dose of 400 mg/m<sup>2</sup> is recommended. Doxorubicin dosage should be reduced if the bilirubin is elevated as follows: serum bilirubin 12 to 30 mg/l - give 1/2 of the normal dose, bilirubin > 30 mg/l - give 1/4 of the normal dose.

In general, impaired renal function does not require dose reduction.

Doxorubicin may be given by intravenous bolus injection, or as continuous infusion. Bolus injection causes higher peak plasma concentrations and therefore is probably more cardiotoxic.

Doxorubicin should not be administered intramuscularly or subcutaneously.

Intravenous administration occurs preferably through a running intravenous infusion, over 3 to 5

minutes.

Patients at increased risk for cardiotoxicity should be considered for treatment with a 24 hours continuous infusion, rather than bolus injection. In this way, cardiotoxicity may be less frequent, without a reduction in therapeutic efficacy. In these patients, the ejection fraction should be measured before each course.

**Dosage in children:**

Dosage in children may be lowered, since they have an increased risk for late cardiotoxicity. Myelotoxicity should be anticipated, with nadirs at 10 to 12 days after start of treatment, but is usually followed by a rapid recovery due to the large bone marrow reserve of children as compared to adults.

**Superficial bladder carcinoma and bladder carcinoma in situ:**

The recommended dosage is 50 mg in 50 ml normal saline, administered via a sterile catheter. Initially, this dose is given weekly, later on, monthly. The optimal duration of treatment has not yet been determined; it ranges from 6 to 12 months.

Restrictions regarding the maximal cumulative dose, as with intravenous administration, do not apply to intravesical administration, because systemic absorption of doxorubicin is negligible.

4.3 Contraindications

Myelosuppression, pre-existing heart disease, previous treatment with complete cumulative doses of doxorubicin or other anthracyclines.

Doxorubicin should not be used intravesically for the treatment of bladder carcinoma in patients with urethral stenosis who can not be catheterised.

4.4 Special warnings and precautions for use

Nausea, vomiting and mucositis are often severe and should be treated appropriately.

Doxorubicin should not be administered intramuscularly or subcutaneously.

Extravasation results in a severe and progressive tissue necrosis. If extravasation occurs, the injection should be terminated immediately and restarted in another vein. Flooding with normal saline, local infiltration with corticosteroids, or sodium hydrogen carbonate solution (8.4%), and application of dimethylsulphoxide have been reported with varying success. The advice of the plastic surgery consultant should be asked for, and wide excision of the involved area should be considered. Exceeding the maximum cumulative dose of 550 mg/m<sup>2</sup> increases the risk of severe, irreversible and therapy-resistant cardiomyopathy and resulting congestive heart failure. Age over 70 or below 15 years should be considered a risk factor, as well as concomitant heart disease. In addition, ECG changes may occur including a reduction in the voltage of the QRS wave, and a prolongation of the systolic time interval, and the ejection fraction may be reduced.

In patients previously treated with other anthracyclines or cyclophosphamide, mitomycin C or dacarbazine and patients who received radiotherapy to the mediastinal area, cardiotoxicity may occur at doses lower than the recommended cumulative limit.

Acute severe arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

Heart function should be assessed before, during and after doxorubicin therapy, e.g., by ECG, echocardiography or determination of the ejection fraction.

The high incidence of bone marrow depression requires careful haematologic monitoring. Doxorubicin therapy should not be started or continued when polynuclear granulocyte counts are below 2000/mm<sup>3</sup>, except in the treatment of acute leukaemia, where lower limits may be applied. Careful haematologic monitoring is also required because of the risk of secondary leukaemias after treatment with cytotoxic agents (see section 4.8 "Undesirable effects"). These leukaemias can be cured when detected at an early stage.

Hepatic function should be evaluated before and during therapy.

Doxorubicin may induce hyperuricemia. The blood uric acid level should be monitored; sufficient fluid intake should be ascertained (with a daily minimum of 3 l/m<sup>2</sup>). If necessary, a xanthine-oxidase inhibitor (allopurinol) may be administered.

Men as well as women should take effective contraceptive measures during and for at least 3 months after doxorubicin therapy.

Doxorubicin may impart a red coloration to the urine.

#### 4.5 Interaction with other medicaments and other forms of interaction

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, mitomycin C, dacarbazine, dactinomycin and, possibly, cyclophosphamide.

Doxorubicin may cause exacerbations of haemorrhagic cystitis caused by previous cyclophosphamide therapy.

The effects of radiation may be enhanced, and recall of these reactions may occur with doxorubicin therapy, even some time after termination of radiotherapy.

Inducers of the enzyme cytochrome P-450 (e.g. rifampicin and barbiturates) may stimulate the metabolism of doxorubicin, with a possible decrease in efficacy.

Inhibitors of cytochrome P-450 (e.g. cimetidine) may decrease the metabolism of doxorubicin, with a possible increase in toxic effects.

#### 4.6 Pregnancy and lactation

Clinical evidence suggests a possible adverse effect on the foetus. In animals doxorubicin has embryotoxic and teratogenic effects.

Doxorubicin is excreted in breast milk. Usage during pregnancy and lactation is therefore not recommended.

#### 4.7 Effects on ability to drive and to use machines

Due to the frequent occurrence of nausea and vomiting, driving and operation of machinery should be discouraged.

#### 4.8 Undesirable effects

Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity. Myelosuppression includes a transient leukopenia, anemia and thrombocytopenia, reaching its nadir at 10 to 14 days after treatment.

Cardiotoxicity may occur as arrhythmia directly following drug administration; ECG changes, including T-wave flattening and S-T depression, may last up to 2 weeks after administration.

The risk of cardiomyopathy increases at cumulative doses higher than 550 mg/m<sup>2</sup>. Age over 70 or below 15 years should be regarded as a risk factor. Also, concomitant or previous treatment with mitomycin C, cyclophosphamide or dacarbazine has been reported to potentiate doxorubicin induced cardiomyopathy.

Cardiotoxicity may be encountered several weeks or months after discontinuation of doxorubicin therapy.

Other adverse reactions reported are: a generally reversible alopecia; gastrointestinal disturbances, including nausea, vomiting and diarrhea. Mucositis (stomatitis or esophagitis) may occur 5 to 10 days after administration.

Hypersensitivity reactions, such as fever, urticaria and anaphylaxis have been occasionally reported. Doxorubicin influences and potentiates normal tissue reactions to radiation. Also, late ("recall") reactions may occur when doxorubicin is administered some time after irradiation.

Facial flushing may occur if the injection is given too rapidly.

Thrombophlebitis and conjunctivitis have been reported.

Slight transient increases of liver enzymes have been reported. Concomitant irradiation of the liver may cause severe hepatotoxicity, sometimes progressing to cirrhosis.

As with other cytotoxic agents, myelodysplastic syndrome and acute myeloid leukaemia have been observed after treatment with combination therapy including doxorubicin. With topoisomerase II inhibitors, secondary leukaemias have been reported more frequently than expected in the form of acute myeloid leukaemia classification 2, 3, and 4. These forms of leukaemia can have a short period of latency (1 to 3 years). They can be cured when detected at an early stage and with an appropriate curative treatment (see section 4.4 "Special warnings and special precautions for use").

Intravesical administration may cause the following adverse reactions: haematuria, vesical and urethral irritation, stranguria and pollakisuria. These reactions are usually of moderate severity and of short duration.

Intravesical administration of doxorubicin may cause a sometimes hemorrhagic cystitis; this may cause a decrease in bladder capacity.

Doxorubicin may impart a red colouration to the urine.

#### 4.9 Overdose

Acute overdosage of doxorubicin enhances the toxic effects of mucositis, leukopenia and thrombocytopenia. Overdosage at intravesical administration may cause severe cystitis. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics and transfusions after consultation with an oncologist.

Chronic overdosage with cumulative doses exceeding 550 mg/m<sup>2</sup> increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations and diuretics.

Administration of a very high single dose may cause myocardial degeneration within 24 hours.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Animal studies have shown a cytotoxic action in several solid and haematologic tumours. The mechanism of action is not completely elucidated. A major mechanism is probably inhibition of topoisomerase II, resulting in DNA breakage. Intercalation and free-radical formation is probably of minor importance. Drug resistance, due to increased expression of the MDR-1 gene encoding for a multidrug efflux pump, has been reported regularly.

### 5.2 Pharmacokinetic properties

The intravenous administration of doxorubicin is followed by a rapid plasma clearance ( $t_{1/2} \approx 10$  min.) and significant tissue binding. The terminal half-life is approximately 30 hours.

Doxorubicin is partly metabolised, mainly to doxorubicinol and to a lesser extent, to the aglycon, and is conjugated to the glucuronide and sulfate. Biliary and fecal excretion represents the major excretion route. About 5% of the dose is eliminated by renal excretion. Plasma protein binding of doxorubicin ranges from 50-85%. The volume of distribution is 800-3500 l/m<sup>2</sup>.

Doxorubicin is not absorbed after oral administration; it does not cross the blood-brain barrier. Impairment of liver function may decrease the clearance of doxorubicin and its metabolites.

### 5.3 Preclinical safety data

None stated.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride, hydrochloric acid/sodium hydroxide, water for injections.

### 6.2 Incompatibilities

Doxorubicin should not be mixed with 5-fluorouracil or heparin. Contact with aluminium should be avoided.

### 6.3 Shelf-life

Following the special precautions for storage (see section 6.4) the shelf-life of the 5 ml, 10 ml and 25ml vials is 36 months and the shelf life of the 100 ml vial is 24 months as printed on the label.

The injection may be diluted with 0.9% sodium chloride solution or 5% glucose solution.

Chemical and physical in-use stability has been demonstrated for 7 days at room temperature (15-25°C) and 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Doxorubin 0.2% injection should be stored at 2-8°C, protected from light.

### 6.5 Nature and contents of container

Doxorubin 0.2% injection is supplied as a red-orange, sterile solution in injection vials containing 5ml (10 mg), 10 ml (20 mg), 25 ml (50 mg), or 100 ml (200 mg), respectively, of doxorubicin hydrochloride 2 mg/ml.

### 6.6 Instruction for use/handling

Any contact with the solution should be avoided. During preparation and reconstitution a strictly aseptic working technique should be used; protective measures should include the use of gloves, mask, safety goggles and protective clothing. Use of a vertical laminar airflow (LAF) hood is recommended.

Gloves should be worn during administration. Waste-disposal procedures should be taken into account the cytotoxic nature of this substance.

If doxorubicin solution contacts skin, mucosae, or eyes, immediately wash thoroughly with water. Soap may be used for skin cleansing.

## 7. MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.  
Swensweg 5

DOXORUBIN 0.2%  
Solution for Injection

PART I : GENERAL INFORMATION

Date : January 2001

Part I B : Summary of product characteristics

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Postbus 552  
2003 RN Haarlem  
The Netherlands.

8. MARKETING AUTHORISATION NUMBER

PL 4946/0016.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4 January 1996.

10. DATE OF PARTIAL REVISION OF THE TEXT

January 2001

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0900.8V.ES(UK)